

ACTA PÆDIATRICA

REDACTORES:

A. LICHTENSTEIN, STOCKHOLM, A. WALLGREN, STOCKHOLM

REDACTORES:

IN DANIA: BENT ANDERSEN, AARHUS, OLUF ANDERSEN, KØBENHAVN, C. E. BLOCH, KØBENHAVN, P. PLUM, KØBENHAVN. *IN FENNIA:* P. HEINIÖ, HELSINGFORS, V. RANTASALO, HELSINGFORS, C.-E. RÄIHÄ, HELSINGFORS, T. SALMI, ÅBO, ARVO YLPPÖ, HELSINGFORS. *IN HOLLANDIA:* E. GORTER, LEIDEN, CORNELLA DE LANGE, AMSTERDAM, J. VAN LOOKEREN CAMPAGNE, GRONINGEN. *IN NORVEGIA:* TH. FRÖLICH, OSLO, LEIF SALOMONSEN, OSLO, L. STOLTENBERG, OSLO, A. SUNDAL, OSLO, KIRSTEN UTHEIMTOVERUD, OSLO. *IN SUECIA:* C. GYLLENSWÄRD, UPPSALA, N. MALMBERG, STOCKHOLM, STURE SIWE, LUND, WILHELM WERNSTEDT, STOCKHOLM, Y. ÅKERRÉN, GÖTEBORG.

REDIGENDA CURAVIT

A. LICHTENSTEIN

KRONPRINSESSAN LOVISAS BARNSJUKHUS,
STOCKHOLM

Vol. XXXIII

MCMXLV—MCMXLVI

Almqvist & Wiksells Boktryckeri Aktiebolag
UPPSALA 1945—1946



Bind suppl. separately

ACTA PÆDIATRICA

REDACTORES

IN DANIA: BENT ANDERSEN, AARHUS, OLUF ANDERSEN, KOBENHAVN, C. E. BLOCH, KOBENHAVN, P. PLUM, KOBENHAVN. *IN FENNIA*: P. HEINIÖ, HELSINGFORS, V. RANTASALO, HELSINGFORS, C.-E. RÄIHÄ, HELSINGFORS, T. SALMI, ÅBO, ARVO YLPPÖ, HELSINGFORS. *IN HOLLANDIA*: E. GORTER, LEIDEN, CORNELIA DE LANGE, AMSTERDAM, J. VAN LOOKEREN CAMPAGNE, GRONINGEN. *IN NORVEGIA*: TH. FRÖLICH, OSLO, LEIF SALOMONSEN, OSLO, L. STOLTENBERG, OSLO, A. SUNDAL, OSLO, KIRSTEN UTHEIMTOVERUD, OSLO. *IN SUECIA*: C. GYLLENSWÄRD, UPPSALA, I. JUNDELL, STOCKHOLM, A. LICHTENSTEIN, STOCKHOLM, N. MALMBERG, STOCKHOLM, STURE SIWE, LUND, ARVID WALLGREN, STOCKHOLM, WILH. WERNSTEDT, STOCKHOLM, Y. ÅKERREN, GÖTEBORG.

EDITOR: I. JUNDELL, STOCKHOLM

Vol. XXXIII. Fasc. 1

31: X. 1945

Almqvist & Wiksells Boktryckeri Aktiebolag
UPPSALA 1945

ACTA PÆDIATRICA

EDITOR PROFESSOR I. JUNDELL

23 ARTILLERIGATAN, STOCKHOLM

The 'ACTA PÆDIATRICA' contain articles relating to pediatrics. These articles are published in English, French or German, according to the wishes of the author. Each number consists of about 6 printed sheets, 4 numbers forming a volume. The numbers will be issued as soon as the articles sent in can be printed. The 'Acta' is open to articles from foreign authors in all countries, if sufficient space can be found for them. Manuscripts are to be sent direct to the Editor, to whom also enquiries about the exchanging of papers are to be directed. The subscription should be forwarded to the Editor. Each volume costs 20 Swedish crowns or 25 shillings or 5 dollars.

ACTA PÆDIATRICA enthalten Arbeiten aus dem Gebiete der Kinderheilkunde. Die Arbeiten werden, je nach eigener Wahl des Verfassers, in deutscher, französischer oder englischer Sprache veröffentlicht. Jedes Heft enthält circa 6 Druckbogen; 4 Hefte bilden einen Band. Die Hefte erscheinen, je nachdem die in dieselben aufzunehmenden Aufsätze druckfertig vorliegen. Die Acta nehmen nach Möglichkeit auch Arbeiten ausländischer Verfasser aller Nationen auf. Manuskripte nimmt der Herausgeber entgegen, desgleichen Wünsche betreffs Austausch von Zeitschriften. Abonnementanmeldung bei dem Herausgeber. Preis pro Band 20 schwedische Kronen.

Les ACTA PÆDIATRICA contiennent des ouvrages du domaine de la pédiatrie. Les études sont publiées en français, anglais ou allemand au choix de l'auteur. Chaque fascicule contient env. 6 feuilles in -8°; 4 fascicules forment un volume. Les fascicules paraissent au fur et à mesure que les articles y destinés sont imprimés. Les Acta reproduisent, dans la mesure du possible, les articles d'auteurs étrangers de tous les pays. Les manuscrits doivent être expédiés à l'éditeur, à qui les demandes relativement à l'échange de journaux devront également être adressées. Abonnement chez l'éditeur. Prix par volume Cr. Suéd. 20.

ACTA PÆDIATRICA





Svenn Monrad †.

19.8.1867 — 18.1.1945.

IN SVENN MONRAD, Scandinavian pediatrics has lost one of its leading men. His eminent ability and intense interest in pediatrics was devoted first and foremost to his own country, Denmark, but with his untiring energy he also found time to take a prominent part both in Scandinavian and international pediatric collaboration.

MONRAD's scientific contributions belong entirely to the field of clinical pediatrics and relate to appendicitis in children, intussusception, diseases of the digestive tract, exsudative diathesis, epilepsy in children etc. With his keen power of observation, his interest in direct study of the child and his clear, pregnant exposition he resembled the French clinician of the classical type. He was less interested in modern laboratory medicine. He was brilliant as a teacher in the clinic of Dronning Louises Børnehospital (Queen Louise's Children's hospital) where for 34 years he worked as head doctor. His

natural eloquence made it a real pleasure to listen to him. At his clinic MONREAD trained a series of disciples, several of whom now occupy leading positions in Danish pediatrics. Beside his hospital work he had a large pediatric practice and was frequently consulted on the subject from all parts of Denmark.

Social pediatrics had an ardent sponsor in MONREAD and, as a member of the Danish Medical Council, he made very considerable contributions in this field.

In the field of Scandinavian pediatric collaboration, which flourished during the inter-war period, MONREAD held a leading position. He was amongst those who took the initiative in forming Nordisk Pediatrisk Förening (the Nordic Pediatric Association), and was for many years a member of its committee. At our congresses, where he was always present, his contributions were greatly appreciated by his audience. Ever since 1921, when the editorial staff of *Acta Pædiatrica* was constituted, MONREAD was a member of it.

In cooperation with TH. FRÖLICH and the author of this memorial, he published in 1941 the first Scandinavian textbook of pediatrics and at the time of his death he was engaged on the 2nd edition.

For many years MONREAD was an important link between Scandinavian and international pediatrics. He had good friends amongst the leading pediatricians in many countries and kept up an animated correspondence. At international congresses and conferences MONREAD's knowledge of languages, the ease with which he expressed himself and his remarkable capacity for making friends always secured for him a leading position. In London and Paris, in Rome and the Hague he was listened to with great interest and respect. In 1931 he was also amongst the founders of Association Internationale de Pédiatrie Préventive, a union for the study of prophylactic pediatrics. In this association he played an important part and at the last meeting in Rome 1938 he was elected its president. The intention was to locate the next congress in Copenhagen, but these plans were frustrated by the war.

Few people have worked harder than MONRAD, but yet he was a man who enjoyed life, who liked to drink a good glass of wine in the midst of his friends where the toil of the day was forgotten and gay chat and witty sallies predominated.

MONRAD is an honour to the pediatrics not only of Denmark, but of Scandinavia at large. He will be long remembered and greatly missed by his numerous friends.

A. Lichtenstein.

FROM THE PEDIATRIC DEPARTMENT OF THE RIGSHOSPITAL, COPENHAGEN, HEAD: PROFESSOR P. PLUM, M. D., AND FROM THE CHILDREN'S HOSPITAL AT FUGLEBAKKEN, COPENHAGEN, HEAD: V. POULSEN, M. D.

The Prognosis for Bronchial Asthma Arisen in Infancy, After the Nonspecific Treatment Hitherto applied.

(An Investigation in the Fate of 298 Asthmatic Children.)

By

E. WINGE FLENSBORG.

The writer's purpose with the present work was to endeavour finding out what chances of recovery there were for bronchial asthma arisen in infancy and treated with the therapeutic methods hitherto applied in Denmark, in order to obtain a material of comparison for estimating the specific, desensitizing treatment applied, since 1943, in the pediatric department of the Rigshospital and, later, both in the clinic for asthmatic children of the Rigshospital and in the children's hospital at Fuglebakken.

Originally it was intended, partly, to send lists of queries to asthma patients who had previously stayed in the mentioned children's departments, partly, to request such patients to report for re-examination. Owing to the conditions in Denmark, with difficulties of travelling etc., however, the latter part of the investigation was rendered impossible.

Previously published investigations in the prognosis for bronchial asthma arisen in infancy.

It is generally believed that the prognosis for asthma arisen in infancy is good, since the majority of the cases will disappear at the age of puberty. MONRAD (11) thus reports that »a great many cases of asthma are cured spontaneously at puberty», and

that »the prognosis on the whole is good but that it must be made with some reservation for children who present signs of permanent lung emphysema». HOLT & McINTOSH (8) report that the affection shows a decided tendency to decline at puberty. In contradistinction to this assertion RIETSCHEL (12) thinks that prognosis is not very good.

WAJSMANN (15) distinguishes sharply between asthma in young children and babies and asthma in adults with early onset (i. e. asthma arisen in later childhood), and he thinks that the first-named group has a tendency to spontaneous recovery at puberty.

HAMBURGER (7) has re-examined 38 children with asthma, and reports that about half of the cases disappear at the age of puberty.

TUSCHERER (14) has re-examined 152 children who had previously been hospitalised or treated for bronchial asthma or asthma bronchitis in the polyclinic of the Berlin University Children's Clinic. On re-examination the diagnosis proved to have been fallacious in 4 cases and very doubtful in 12 cases, the children in these cases merely having had »asthmatic» manifestations for a very brief period (days or weeks). Among the remaining 136 children were 74 (54 per cent) in whom the attacks and the bronchitis had ceased. TUSCHERER reports that 35 of these children recovered before the age of puberty and 39 recovered later. Exact information about the time of recovery from the affection is missing in TUSCHERER's work, there being very considerable disagreement between the figures reported in the text and the curve plotted for the times of cessation of the disease.

BUCHARDT (3) has made inquiries about 103 asthmatic children who from 18 months to 10 years ago had stayed in the children's sanatorium »Pro Juventute» in Davos (Switzerland), and who had received no treatment besides the stay in the high mountain climate. Eighty-nine children replied to the inquiries. Among these were 26 (29.2 per cent) who had never re-incurred any attacks, and 32 (35.9 per cent) who had experienced permanent improvement as an immediate result of the stay. More exact examinations of the time and percentage of cessation of infantile asthma are not available.

The writer's own investigations.

The material of patients comprises 338 children with bronchial asthma altogether, 256 of whom were admitted to the children's department of the Rigshospital and 82 to the children's hospital at Fuglebakken during the period from 1926 to 1939.

That relatively so many asthmatic children have been examined in the children's ward of the Rigshospital certainly is due essentially to Doctor BAAGØE (1) who in the beginning of the nineteen-twenties took the initiative in that department.

Seventeen of the patients could not be traced through the registry-office or had gone abroad. Thus *there were forwarded 321 lists of inquiry altogether.*

Of these 321 lists of inquiry, 298 were answered satisfactorily, which means a percentage of replies of 92.8. The percentage of replies in proportion to the original material of patients was 88.2. On the ground of the case reports it proved impossible to divide the patients into different groups according to the kind of asthma after the principles which now prevail (see for example BRAY (2)), therefore the material had to be judged collectively.

Distribution according to sex: Of the 298 children 190 (63.8 per cent) were boys and 108 (36.2 per cent) were girls.

TUSCHERER (14) among 152 asthmatic children found 93 boys (61.2 per cent) and 59 girls (38.8 per cent). BRAY (2) found that asthma in children under 10 years of age was 3 times as frequent in boys as in girls. Thus there is no doubt that *infantile asthma occurs much more frequently in boys than in girls*, and, as will be seen later, there is also a difference in the two sexes as regards the moment of onset of the affection and the prognosis.

The moment of onset of the disease.

The result of an investigation in the time of onset of the attacks of asthma was (see Fig. 1 and Table 1) that the great majority of the cases (attacks) commenced before the age of 5 years, namely, 197 out of 298 (66.4 per cent). This corresponds exactly to ЧОБОТ's (4) findings on examining 84 asthmatic children, for in 54 of these (i. e. 69 per cent) the attacks commenced before the patients were 5 years old.

Table 1.

Age of onset of first attack of asthma in 298 children.

Age of onset of first attack of asthma	Number of children whose attacks commenced at the recorded ages	Number of boys	Number of girls
< 1 year	20	11	9
1 »	50	34	16
2 years	47	32	15
3 »	41	24	17
4 »	39	25	14
5 »	26	18	8
6 »	27	18	9
7 »	16	10	6
8 »	16	8	8
9 »	10	4	6
10 »	3	3	0
11 »	2	2	0
12 »	0	0	0
13 »	0	0	0
14 »	1	1	0
Total	298	190	108

The age of onset of the first attack of asthma in most cases was the 2nd and 3rd year of life (50 and 47 cases, respectively). JUMON (9) found that most of the first attacks of asthma occurred at about the third year of life.

Generally attacks of asthma in infancy are regarded as being very rare. FINKELSTEIN (5) thought that true attacks of asthma did not occur in infants at all, in the literature, however, a good many such cases are on record (CHOBOT (4), GIRLEA & BOGDAN (6), LOOKEREN (10), and STÄUBLI (13)). It is emphasized that it may be very difficult to make a diagnosis, the disease at that age easily being mistaken for pneumonia, capillary bronchitis, bronchotetany, glandular tuberculosis, thymus hypertrophy, and congenital heart disease with cardiac insufficiency associated with asthmatic dyspnea.

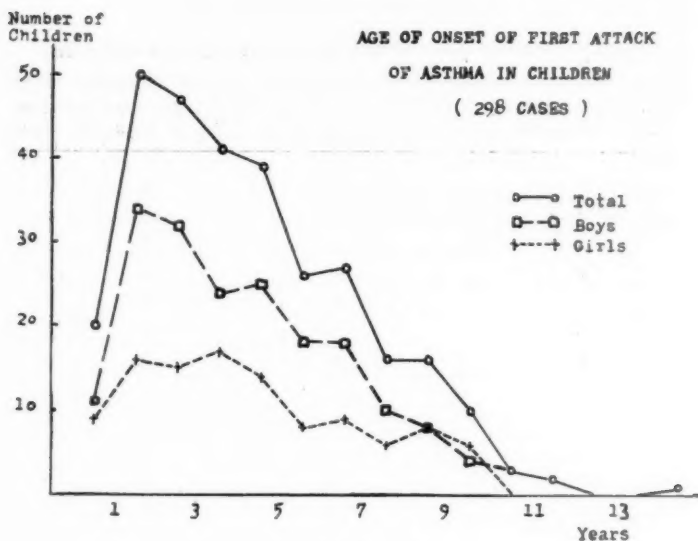


Fig. 1.

The 20 cases of attacks of asthma incurred in the first year of life which are recorded in this material may, as far as the case reports are concerned, be regarded as reliable, so much the more as the attacks of asthma in 19 of them continued for several years. In 8 of these children the attacks ceased at the age of from 4 to 12 years, whereas 10 patients, at the time of the research, still had attacks at the age of from 8 to 25 years. One of the children died 1 year old, and one at the age of 16 years (at that time still suffering from asthma).

As is evident from Fig. 1, there is some difference in boys and girls as regards the time of onset of the attacks of asthma:

Both for boys and girls it holds that the attacks in about $\frac{2}{3}$ of the cases commenced before the age of 5 years (boys 66.4 per cent, girls 66.3 per cent), the curve of the boys however presenting a pronounced maximum corresponding to the 2nd and 3rd years of life, which is not so pronounced for the girls.

If the onset of the disease is calculated from the onset of bronchitis in those cases in which bronchitis preceded the attacks of asthma proper, the distribution is as follows (Table 2):

Table 2.

Age of onset of first attack of asthma or asthmatic bronchitis.

Age of onset of first attack of asthma	Number of children whose attacks commenced at the recorded ages	Per cent	Number of boys	Number of girls
< 1 year	46	15.4	31	15
1 "	59	19.8	41	18
2 years	59	19.8	37	22
3 "	41	23.8	22	19
4 "	28	9.4	20	8
5 "	15	5.0	8	7
6 "	18	6.0	11	7
7 "	15	5.0	9	6
8 "	7	2.3	4	3
9 "	6	2.0	3	3
10 "	2	0.6	2	0
11 "	1	0.3	1	0
12 "	0	0.0	0	0
13 "	0	0.0	0	0
14 "	1	0.3	1	0
Total	298	—	190	108

A glance at Table 2 and Fig. 2 shows that, if the inception of bronchitis is regarded as onset of the disease, and in those cases in which the first attack of asthma is not preceded by bronchitis, this first attack is regarded as onset of the asthma, *the disease in the great majority of the cases commences before the age of 5 years, namely, in 78.4 per cent.* The age of onset of the first attack of asthma was under 5 years in 79.5 per cent of the boys and in 76.6 per cent of the girls.

A similar result is reported by TUSCHERER (14) who found that the disease (bronchitis or attacks of asthma) in 110 out of 152

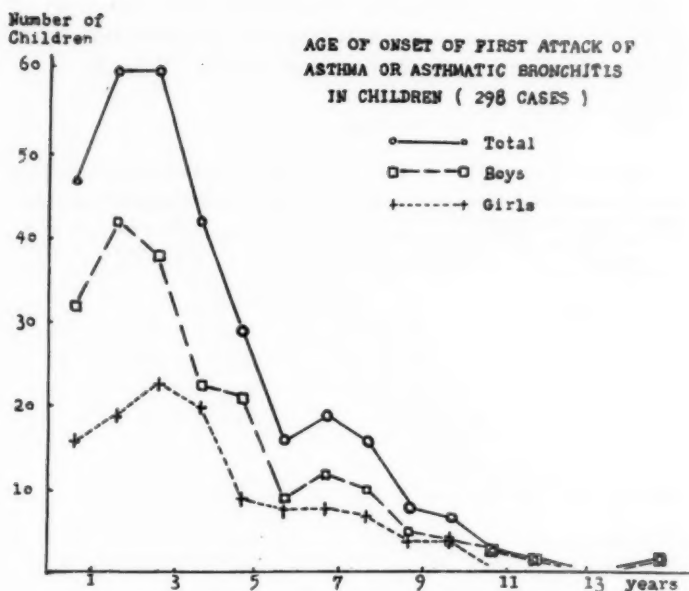


Fig. 2.

asthmatic children (i. e. in 73 per cent) commenced before the age of 5 years. BRAY (2) showed that, among 1390 cases of asthma with ages of onset of from 0 to 10 years, 22.25 per cent commenced in the first year of life, 17 per cent in the second, 13.5 per cent in the third, 10.75 per cent in the fourth, 10.25 per cent in the fifth, 8.5 per cent in the sixth, 6.25 per cent in the seventh, 5.5 per cent in the eighth, 4.25 per cent in the ninth, and 1.75 per cent in the tenth year of life.

The distribution of the 298 patients who replied to the list of queries was as follows (Table 3).

In the following each group of children will be discussed separately.

Table 3.

	The total material		B o y s		G i r l s	
	Number of children	Per cent	Number of boys	Per cent	Number of girls	Per cent
Attacks ceased	120	40.3	75	39.5	45	41.7
Still attacks	163	54.7	108	56.8	55	50.9
Deaths	15	5.0	7	3.7	8	7.4
Total	298	100.0	190	100.0	108	100.0

(1) Attacks ceased at the time of inquiry.

The attacks are regarded as having ceased in those patients who have had none for at least 1 year. This is a fairly casual limit, nor is it in reality sure enough, as is evidenced by a number of examples in the very material (attacks ceased and recurred after the lapse of varying numbers of years — see later under (2)). The children's ages at the time of cessation of the attacks of asthma are recorded in Table 4.

Table 4 shows that *the attacks of asthma in boys oftenest cease at the age of 12—15 years inclusively, whereas, in girls, the most common age of cessation of the attacks is between 9 and 12 years.*

Thus the girls' attacks generally cease somewhat earlier than the boys' attacks, which is also evidenced by the fact that, in 32 of 45 girls (71.1 per cent), they ceased before the age of 13 years, whereas that only happened in 42 of 75 boys (54.7 per cent).

The attacks of asthma had thus ceased in about 40 per cent of the children at the time of inquiry. Not all the children had become so old, however, that it might not be reckoned with that a greater or smaller number of them in the future could become free from attacks. It will therefore be of interest to find out the percentage of cessation for those patients who, at the time of inquiry, were 18 years old or more. *131 of the children had reached an age of 18 years or more. In 58 of these i. e. in 41.1 per cent, the attacks*

had ceased. In 46 of the 106 patients, i. e. in 43.2 per cent of them, who had attained an age of 20 years or more, the attacks had ceased.

Table 4.

Times of cessation of attacks of asthma in 120 children with asthma.

Age (years)	Number of children whose attacks ceased at the recorded ages	Number of boys	Number of girls
2	5	4	1
3	2	1	1
4	5	3	2
5	4	3	1
6	6	3	3
7	10	6	4
8	5	5	0
9	9	4	5
10	7	2	5
11	10	4	6
12	11	7	4
13	5	4	1
14	13	10	3
15	9	7	2
16	1	1	0
17	8	6	2
18	2	2	0
19	1	1	0
20	1	0	1
21	2	1	1
22	0	0	0
23	0	0	0
24	1	1	0
No exact information about the time	3	0	3
Total	120	75	45

Possible causes of the cessation of the attacks.

To obtain information, if possible, about eventual factors of importance for the prognosis of infantile asthma the afore-mentioned list of queries contained the following questions:

(a) Did the attacks cease when the patient moved to another place?

(b) If not, could you then fancy a special cause of the cessation of the attacks?

The following factors were mentioned by the patients or their relatives as probable causes of the cessation of the attacks:

(1) Attacks ceased after the patient's removal to another place in the country or to another flat in the same town	31
(2) No attacks since patient's discharge from hospital ..	10
(3) Sanitation of lodgings or room (according to directions from the hospital)	9
(4) Spray treatment	3
(5) Stay at some health resort or sanatorium for children ..	2
(6) Much sport and open-air existence	2
(7) Dietary treatment	2
(8) Corset treatment	2
(9) Respiration gymnastics	1
(10) Vaccination against »colds»	1
(11) Attacks ceased after whooping cough	1
(12) Attacks ceased after rheumatic fever	1
(13) No probable cause of the cessation of the attacks known	49
(14) No information	6
<hr/>	
Total	120

The causes (2) and (3) may in reality be regarded as identical, for the reason why the children have had no attacks since their discharge from hospital probably is that the parents have followed the directions given by the hospital with regard to the arrangement of their bed-rooms and beds. As the removal to another place or another flat may also be regarded as a kind of sanitation of

lodgings, it means that *no less than 50 of the 120 children (41.7 per cent) whose attacks of asthma have ceased, have recovered from their disease by changes of residence.*

The duration of the disease in the 120 children whose attacks had ceased at the time of inquiry.

A glance at the moments of onset and of cessation of the attacks of asthma in boys as well as in girls seems to show that, in those cases in which the attacks had ceased at the time of inquiry, the disease was of somewhat longer standing in the boys than in the girls.

Therefore a closer examination of the duration of the disease both in the boys and in the girls was performed. Exact information about the moments of onset and of cessation of the attacks were missing in 4 of the 120 children whose attacks had ceased at the time of inquiry. In the remaining 116 children *the average duration of the disease was 7.4 years, i. e. in the boys it was 7.7 years, and in the girls 6.9 years*, the duration of the disease varying exceedingly, however, as is shown in Table 5.

The duration of the disease was calculated from the onset of the attacks of asthma, and not from the inception of an eventually preceding asthmatic bronchitis, because it proved to be more difficult to determine this latter moment exactly.

As was already mentioned prefatorily, the writer's intention was also to re-examine the children with special regard to how many of the patients whose attacks ceased still had emphysema or chronic bronchitis and who, despite the cessation of the attacks, were tainted by the disease of their childhood. As the re-examination had to be given up, only the patients' own information about their eventual symptoms from the respiratory tract afforded a clue to the elucidation of the question.

Of the 120 patients, whose attacks had ceased at the time of inquiry, 8 patients reported having a cough also when they had not caught cold, 5 patients complained of constant expectoration, and no less than 53 patients (44.2 per cent) suffered from dyspnea.

Table 5.

Duration of the disease in 116 asthma patients whose attacks had ceased at the time of inquiry.

Duration of the disease (years)	Number of children	Number of boys	Number of girls
1	10	8	2
2	7	3	4
3	7	3	4
4	8	3	5
5	11	7	4
6	11	7	4
7	9	7	2
8	5	3	2
9	10	5	5
10	14	11	3
11	5	4	1
12	7	5	2
13	5	4	1
14	1	1	0
15	2	0	2
16	1	1	0
17	0	0	0
18	1	1	0
19	2	1	1
Total	116	74	42

In these 53 cases the dyspnea occurred on different occasions. 42 patients reported that the dyspnea was elicited by movement or exertion, in most of them, however, only by strain. 4 patients reported dyspnea both during rest and work though never in the form of attacks. 2 patients suffered from dyspnea when they had caught cold. 2 patients incurred dyspnea when they were exposed to smoke or fog. 2 patients became dyspneic in cold air. 1 patient became dyspneic when gathering seed.

Table 6.

Age distribution for 163 patients still having attacks at the time of inquiry.

Age at the time of inquiry (years)	Number of children	Number of boys	Number of girls
7	3	1	2
8	4	4	0
9	2	1	1
10	12	6	6
11	4	4	0
12	8	7	1
13	13	7	6
14	11	9	2
15	6	4	2
16	11	7	4
17	5	1	4
18	11	5	6
19	13	12	1
20	7	6	1
21	6	2	4
22	9	4	5
23	11	7	4
24	5	4	1
25	2	1	1
26	2	1	1
27	2	2	0
28	4	2	2
29	5	4	1
30	3	3	0
31	2	2	0
32	1	1	0
33	1	1	0
Total	163	108	55

As is seen from the above, it is doubtful whether the attacks of asthma in the last 7 cases really may be regarded as having ceased. The patients themselves reported, however, that the attacks had ceased, and those reports have been taken as a basis for the estimation, even though the prognosis for asthmatic children thus has become too favourable.

That 53 of the 120 children, whose attacks had ceased, constantly suffered from dyspnea, may be interpreted as signifying that several of them at any rate have incurred permanent emphysema or chronic bronchitis in sequel to the asthma which they had now got over. Information as to their exact number naturally is not available.

(2) Patients still having attacks at the time of inquiry.

At the time of inquiry 163 patients, namely, 108 boys and 55 girls, still incurred attacks of asthma. The age distribution is recorded in Table 6.

The frequency of the attacks as compared to the former frequency.

In 14 patients the attacks had become more frequent (8.6 per cent). In 116 patients they had become less frequent (71.2 per cent). In 22 patients the frequency of attacks was unchanged (13.5 per cent). 8 patients had been free from attacks for a considerable number of years, and then had re-incurred attacks (see Table 7) (4.9 per cent). From 3 patients no exact information was obtained.

Five of those 8 patients did not mention any special cause of the recidivation of their disease. One patient declared that the recidivation occurred immediately after his having moved to another flat in an old house. One patient reported that his attacks of asthma ceased after his removal to Norway (the high mountains) when he was 22 years old but that they recurred there 5 years later without any detectable reason. One patient re-incurred attacks after having moved to another town.

Table 7.

Survey of 8 patients whose attacks of asthma had ceased for a number of years and then recurred.

Age of onset of attacks of asthma	Symptom-free period from the	Constant occurrence of attacks at the age of
1 year	15th to 19th year	32 years
2 years	22nd to 27th "	29 "
3 "	5th to 12th "	12 "
4 "	5th to 10th "	10 "
4 "	16th to 28th "	30 "
5 "	12th to 18th "	30 "
5 "	13th to 19th "	19 "
5 "	10th to 19th "	19 "

The intensity of the attacks as compared to previous attacks.

In 21 patients the attacks had become more pronounced (13.5 per cent). In 94 patients they had become less pronounced (57.7 per cent). In 25 patients the intensity of the attacks was unchanged (15.3 per cent). From 15 patients no exact information was obtained. As to 8 of the patients see the preceding section.

Thus, in the majority of the children whose attacks of asthma had not only become less frequent (in 71.2 per cent of them) but also less pronounced (in 57.7 per cent of them); only in a few patients had the attacks become more frequent and more pronounced in the course of time.

Apart from the patients' condition with regard to the attacks of asthma it was of interest to obtain information about their state of health in the periods between the attacks.

The patients' general condition between the attacks.

By 121 of the 163 patients it was reported that their general condition between the attacks was good, 17 patients reporting that it was only partially satisfactory, whereas 15 patients declared

that they felt ill in the intervals between the attacks (10 failed to give information about their general condition).

59 patients (36.4 per cent) reported that there was no dyspnea in the periods between the attacks. 78 patients (47.5 per cent) experienced dyspnea (though in very different degrees) when they moved or worked. 22 patients (13.6 per cent) suffered from dyspnea both at rest and in moving. 3 patients reported that they experienced dyspnea between the attacks, when they were tired or nervous, or in foggy weather. (One patient failed to give information about his general condition.

68 patients (41.7 per cent) reported that they had a cough, and 45 (27.6 per cent) declared that they had expectoration in the intervals between the attacks.

(3) Patients who died before the time of inquiry.

Fifteen children — 7 boys and 8 girls — (5 per cent) died before the time of inquiry.

Five patients, i. e. 1.7 per cent of the total material, died in status asthmaticus at the following ages: 9 months, 5 years, 18 years, 18 years, and 25 years. The remaining 10 patients died of other intercurrent diseases which had nothing to do with asthma.

School-attendance.

Apart from the distress caused a child and its relatives by asthma, the disease is very irksome because of the patient's many and protracted confinements to bed necessitated by it, with imperfect school-attendance entailed by them.

An examination with regard to the patients' school-attendance gave the following result (Table 8):

Of the 139 children (46.6 per cent) whose school-attendance was seriously interfered with by their asthma, 52 were not moved to a higher form once, whereas 9 patients were not moved twice, and 3 children had always to be taught at home. Five children on account of their disease commenced their school-attendance from 1 to 4 years later than in the compulsory 7th year of life.

Table 8.

School-attendance.

School-attendance seriously interfered with	139
School-attendance somewhat interfered with	14
School-attendance slightly or not interfered with at all . . .	101
Deaths (no exact information)	15
No reply to the list of queries	8
No attacks during the time of compulsory school-attendance .	21
Total	298

Choice of a profession.

Among the 298 children which the material comprised were 100 who constantly suffered from attacks and who, at the time of inquiry, were more than 15 years old, besides 16 children whose attacks of asthma had ceased after their 15th year of life. Of these 116 patients, 39 reported that they had chosen a special profession on account of their asthma, 3 of them received an invalid pension, whereas 2 reported that they could not obtain any position because of their disease; 17 (7 per cent) of the patients reported that, on account of their disease, they had been compelled to change from one profession to another, one of them several times, and one patient twice.

Treatment of the examined children.

The treatment of the 298 children has been very different, certain chief lines of direction however being followed in the great majority of the cases. Most of the patients were submitted to cutaneous tests ad modum БАΛΓΘΕ (1), and when they presented pronounced positive reactions, they were advised as far as possible to avoid the respective allergens. Generally the patients received some direction or other with regard to the sanitation of their lodgings or beds, which were not followed in many cases, however. A great many of the children have stayed once or several times in the country (in a country health resort or coast sanatorium for

children), and the majority of them have received carbon arc light treatment at some moment or other of the disease. A minority of the patients have received treatment in the pneumatic chamber or of respiration gymnastics; 14 children were treated with Bisgaard's corset, and in 6 of these the attacks of asthma ceased.

Of 13 children who had received tuberculin treatment in 1926, 2 had got rid of their attacks of asthma, whereas 2 died of another illness.

A few patients were treated with insulin sub-shock, and several of the children had once or several times received short series of ordinary cold vaccine or torantil injections. A few patients were submitted to hormone treatment.

None of the patients had received specific treatment proper. For the sake of completeness it shall be mentioned that several of the patients had consulted a chiropractor or some other quacks, only one of the patients however thought that his condition had been bettered by such treatment.

From the above-recorded facts: (1) that the attacks of asthma are cured spontaneously (or, more correctly speaking, yield to the treatment hitherto applied in Denmark) in no more than 40 per cent of the cases, (2) that they averagely do not cease till 7.4 years after their onset (varying from 1 to 19 years), (3) that the mortality amounts to 1.7 per cent (status asthmaticus) and, finally, (4) that the child and its relatives are greatly distressed by the attacks, the child's protracted confinements to bed with inevitable neglect of school-attendance, and in some cases subsequent invalidism, it is evident that a more active treatment of infantile asthma is very desirable in Denmark.

Summary.

The writer's intention with the present work was to investigate the prognosis for infantile asthma after application of the therapeutic methods hitherto used in Denmark in order to obtain a material of comparison for the estimation of the effect of the specific, desensitizing treatment.

For that purpose lists of queries were sent to 321 patients who had previously been hospitalised for bronchial asthma.

298 patients (92.8 per cent) replied satisfactorily.

- (1) 190 of them (63.8 per cent) were males, and 108 (36.2 per cent) were females.
- (2) In the great majority of the cases the age of onset of the attacks of asthma was below 5 years.

If the first attack of asthma proper was regarded as onset of the disease, 66.4 per cent of the cases commenced before the age of 5 years.

If the inception of an eventually preceding bronchitis was regarded as onset of the disease, 78.4 per cent of the cases commenced before the age of 5 years. Most of the cases commenced at the age of 2—3 years.

- (3) In 120 of the 298 patients the attacks had ceased (40.3 per cent); 15 of them had died (5.0 per cent), and 163 (54.7 per cent) constantly had attacks of asthma. In the boys the attacks mostly ceased at the age of from 12 to 15 years, whereas, in the girls, they generally ceased at the age of from 9 to 12 years.

In 58 (41.1 per cent) of 131 patients who had reached an age of 18 years the attacks had ceased.

In 46 (43.2 per cent) of 106 patients who had attained an age of 20 years or more, the attacks had ceased.

That means to say that it may be reckoned with that some 40 per cent of the cases of infantile asthma are cured spontaneously or by the treatment which has hitherto been applied in Denmark.

- (4) 41.7 per cent of the patients whose attacks of asthma had ceased reported that the cessation was due to removal or to sanitation of their lodgings.

- (5) The average duration of the disease in the 120 cases in which the attacks of asthma had ceased, was 7.4 years (7.7 years for the boys, and 6.9 years for the girls).

- (6) Some 44 per cent of the children whose attacks of asthma had ceased at the time of inquiry, had dyspnea, most of them, however, only on stronger exertion.

- (7) In 71 per cent of the patients whose attacks had not ceased, they had become less frequent, and in 58 per cent of the patients they had become milder. Only in about 10 per cent of the patients the attacks of asthma had become both more frequent and stronger.

(8) The great majority of the patients who continued to suffer from attacks of asthma, felt well in the intervals between the attacks, some 47 per cent, however, suffered from dyspnea (mostly exertion dyspnea only), and some 41 per cent suffered from cough in the intervals.

(9) 5 per cent of the children had died before the time of inquiry, 5 of them (1.7 per cent of the total material of patients) in status asthmaticus.

(10) In 139 of the 298 patients (46.6 per cent) the school-attendance was seriously interfered with on account of the disease.

(11) 33.6 per cent of the 116 patients who continued to incur attacks of asthma after their 15th year of life, or whose attacks had ceased after the 16th year, had, on account of their disease, to choose special professions, and 7 per cent of these were subsequently compelled to change their profession again.

(12) The writer gives a brief survey of the methods of treatment applied.

(13) It is emphasized that a more active therapy of infantile asthma is necessary in Denmark.

References.

- (1) BAAGØE, K.: »Bidrag til Studiet af Asthma, særlig hos Børn». Thesis. Copenhagen 1926. — (2) BRAY, G. W.: *Recent Advances in Allergy*. London 1937. — (3) BUCHARDT, J. L.: *Dauerresultate klinischer Kuren bei kindlichem Asthma*. Schweiz. med. Wschr. Vol. 2, 1194—96, 1932. — (4) CHOBOT, R.: *Asthma in Children. An Analysis of eighty-four Cases*. Am. J. Dis. Child. Vol. 45, 26—31, 1933. — (5) FINKELSTEIN, H.: *Säuglingskrankheiten*. — (6) GIRLEA, J. & L. BOGDAN: *Über kindliches Bronchialasthma*. Arch. Kinderh. Vol. 116, 65—68, 1939. — (7) HAMBURGER, F.: *Asthma im Kindesalter*. Wien. klin. Wschr. Vol. 141, 1. 87—91. — (8) HOLT, L. E. & R. MCINTOSH: *Diseases of Infancy and Childhood*. 11th edition 821. New York—London 1939. — (9) JUMON H.: *L'asthme infantile et les réactions associées*. Monograph. Paris 1931, p. 139 (cit. after Zentralbl. d. ges. Kinderheilk. Vol. 25, 393, 1931). — (10) LOOKEREN CHAMPAGNE, J. VAN: *Asthma bei Säuglingen*. Nederl. Tijdschr. Geneesk. 5469, 74, 1938 (cit. after Centralbl. f. d. ges. Kinderh. Vol. 35, 655, 1939). — (11) MONRAD, S.: *Nordisk Lærebog i Pædiatri*. Copenhagen 1941, Vol. 1, 276. — (12) RIETSCHEL,

H. in FEHR: Lehrbuch der Kinderheilkunde. 12th edition. Jena 1938, 349.
— (13) STÄUBLI, C.: Beitrag zur Kenntnis u. z. Therapie des Asthma. Münch.
med. Wschr., p. 113, 1913. — (14) TUSCHERER, J.: Beitrag zum Asthma
(asthmatische Reaktion) im Kindesalter. Jahrb. f. Kinderheilk. Vol. 127,
20—68, 1930. — (15) WAJSMANN, S.: Sur l'asthme infantile. Thesis. Lau-
sanne 1938, p. 32 (cit. after Zentralbl. d. ges. Kinderheilk. Vol. 37, 518,
1940).

On the genesis of erythroblastosis foetalis.

By

S. RANSTRÖM.

The coining of the term erythroblastosis foetalis (DIAMOND *et al.* 1932) as a collective name for the three disease pictures of hydrops foetalis, icterus gravis neonatorum and anaemia gravis neonatorum, was prompted partly by their similar patho-anatomical picture with abundance of extramedullary haemopoietic foci, and partly by the clinical finding of erythroblasts in the circulating blood of the child. A genetic relationship between the three diseases, which are so different from another clinically, was made probable by the tendency towards familial occurrence, where they often alternate in one and the same group of sibs. The most recent literature has been inclined to abandon the above-mentioned designation, and instead introduce the collective term of »haemolytic disease of the newborn». This is due to the modern theory of an iso-immunisation as the common cause of the three diseases, which consists in the formation in the maternal organism of haemolysins against the blood corpuscles of the foetus.

No detailed review of previously advanced theories will be given here; readers are referred to BROMAN's monograph of 1944, which is nevertheless incomplete on a number of points (see below).

After LEVINE *et al.* (1940) had advanced the theory of an Rh iso-immunisation as the genesis of erythroblastosis foetalis, this was almost immediatly accepted as the definitely established cause of disease — at all events to judge from the literature. A number of authors, mainly American and English, have made

considerable clinical investigations based on this theory, and no dissentient voices have been raised against it in the literature.

The theory is this: The mother should belong to the blood group Rh(—) and the foetus to the group Rh(+); by receiving blood corpuscles from the foetus, the mother forms an anti-Rh factor, which is in its turn transmitted to the foetus and haemolyses its blood, with a »*morbus haemolyticus*» as result. Some approximate figures from the literature should also be quoted: 85 % of mankind is Rh(+); the combination of mother Rh(—) — foetus Rh(+) occurs in every 10th delivery; erythroblastosis occurs in about 1 case in 500, from which follows that erythroblastosis appears only in every 50th case of the regular blood group combination. In about 90 % of the erythroblastosis cases, the mother belonged to the Rh(—) group, and in practically all cases the child was Rh(+). The anti-Rh factor could be demonstrated in the mother in 50—90 %; BROMAN, however, asserts that this factor appears to far more than 90 % in classical cases of »familial» erythroblastosis.

These figures immediately prompt a number of questions. Firstly: Why is erythroblastosis found only in every 50th case of the typical blood group combination, and iso-immunisation even less frequently? Secondly: Why cannot the anti-Rh factor be demonstrated in all cases of erythroblastosis? And finally: If an Rh iso-immunisation is the crucial factor in the genesis of the disease, why does one not always have the typical blood group combination? The first question is of great interest, as it can hardly be answered except by the assumption of a primary placental lesion; as is known, a normal placenta allows no transference of blood corpuscles from the foetal to the maternal vascular system. Thus, a placental lesion is an indispensable prerequisite of an iso-immunisation. The two last questions are answered by the theoretical speculation that there are other causes of iso-immunisation than the Rh system. Incidentally, it should also be pointed out here that the literature contains descriptions of cases where anti-Rh factor was demonstrated in the mother, while the child was healthy (BURNHAM, RACE *et al.*, LANGLEY & STRATTON); this might be thought due to the placenta's having

on some occasion allowed the passage of red corpuscles from foetus to mother, the lesion being repaired before the anti-Rh factor had time to form — this if one wishes to set the great store by Rh iso-immunisation which the modern literature does.

Starting from the iso-immunisation theory, the obscurest and most complicated circumstance is that, in erythroblastosis, practically all foetuses are born at term, and that the dangerous symptoms appear in association with or after delivery; this also holds for hydrops foetalis, though here stillbirths are the rule. BROMAN also asserts that there is no connection between early death of the foetus and Rh iso-immunisation. If an iso-immunisation were the cause of the disease, we should instead expect a considerable improvement in the state of the foetus with birth, when it escapes from the supply of the injurious substance present in the mothers blood. The fact that the foetuses do not die far earlier in pregnancy is explained by BROMAN in two ways. The first possibility which, however, he considers on good grounds to be not very probable, is that the placenta is not permeable by the anti-Rh factor until far on in pregnancy. The second possibility corresponds to the theoretical speculation of the presence of a protective substance which is formed in the mother's organism, transmitted to the foetus, and which prevents haemolysis of its blood. Here BROMAN makes the bold assumption that a hormone might have this effect.

It thus remains to explain 1) why signs of Rh iso-immunisation are absent in a number of cases of erythroblastosis, 2) why Rh iso-immunisation can be shown to be present without erythroblastosis, and 3) why the clinical course of the disease is not satisfactorily explained by the Rh iso-immunisation theory.

The theory that Rh iso-immunisation is the main cause of erythroblastosis is also difficult to reconcile with the pathological changes. It is true that the changes in the bone marrow, the extramedullary haemopoiesis and the deposits of iron in a number of organs (above all liver and spleen) can be easily explained as reactions to and consequences of increased decomposition of blood (though it may be noted that the combination of

erythroblastosis and normal haemoglobin value with lethal issue is not at all rare).

However, even before the Rh theory was advanced as a general explanation of erythroblastosis, a group of patho-anatomical changes of a completely different kind had been observed, which could not very well be assumed secondary to an iso-immunisation with accompanying decomposition of blood. A number of authors have observed changes in certain of the endocrine organs, and their data have been more or less consistently disregarded by those authors (including BROMAN) who approached the problem from the angle of the Rh theory, and who in so doing practically completely neglected to take the patho-anatomy of the disease into account.

An insular hyperplasia in the pancreas with hyperinsulinism without diabetes in the mother has been demonstrated by LIEBEGOTT (1938) in hydrops foetalis, and by BENEKE (1939) in icterus gravis neonatorum. These authors also demonstrated an adrenocortical hyperplasia due to a thickening of and abundant deposition of lipoids in the reticular zone. BENEKE does not consider these changes to have genetic importance for erythroblastosis, but to be participating phenomena in a general »keimbedingter Hemmungs- und Fehlbildung».

BURGER (1938) and VON PALLOS (1939) have had opportunity of investigating ovaries from mothers who had borne foetuses with erythroblastosis. In both these cases there were large corpus luteum cysts, in VON PALLOS's case containing large quantities of gonadotropic hormone and oestrone.

When making hormone investigations of the placenta in cases of erythroblastosis, TSCHERNE (1938) found a great increase of the oestrone content — 130 000 M. U. instead of the normal 5 000 M. U. On the other hand, HERRNBERGER (1940) and ZIGMOND (1941) found a similar investigation to yield normal values for the oestrone, but to show an abnormal abundance of gonadotropic hormone in the placenta. These authors also found great quantities of gonadotropic hormone in the urine from the mothers of erythroblastotic children.

A particularly interesting fact is that HELLMAN & HERTIG

(1938) were able to show intense and constant placental changes in a material of 23 cases of erythroblastosis (16 cases of hydrops, 7 cases of icterus gravis). These changes consisted of a considerable increase in the placental weight, enlarged villi, degeneration of the syncytial cell layer, persistence of Langhans's layer, hypertrophic and oedematous stroma with atrophic vessels and haemopoietic foci.

In this paper, the author can supplement such cases with changes of endocrine nature in erythroblastosis by another two, which in addition to adrenal hyperplasia and, in one case, insular hyperplasia in the pancreas, showed pituitary changes hitherto not described.

Case histories.

Case I. Mother healthy. Third child (sibs: I prematurely born [weighed 900 gm], died after 2 days; II healthy). Hydropic, full-term, male foetus, died during partus. The autopsy revealed no noteworthy changes in the central nervous system or the circulatory and respiratory organs. The liver, which was perceptibly enlarged (200 gm) proved on histological examination to be the seat of a massive deposition of haemopoietic elements, and so did the spleen. Together, the adrenals weighed 14.5 gm (about double the normal weight); the reticular zone was greatly thickened and showed abundant infiltration of lipoids. There was no certain insular hyperplasia in the pancreas. The hypophysis which was of normal size, proved on histological examination to contain such an abundance in basophile cells that it gave the impression of an adult organ. — The placenta, which weighed 1 200 gm, was unfortunately not examined histologically.

Case II. Mother healthy. Third child (sibs: I healthy; II died during partus, cause unknown). Hydropic, full-term, female foetus died during partus. The autopsy revealed nothing unusual in the central nervous system, or in the circulatory and respiratory organs. The liver and spleen were moderately enlarged; histological examination revealed abundant infiltration of haemopoietic foci. The adrenals were considerably enlarged (14 gm), due to a thickening of and abundant deposition of lipoids in the reticular zone. There was a great insular hyperplasia in the pancreas. Histological examination of the hypophysis showed increase of the basophile cells which, though moderate, was perceptibly pathological. — The placenta (950 gm) was not histologically examined in this case, either.

According to KRAUS (1926), the basophile cells in the foetal hypophysis start forming towards the end of the pregnancy, or not until after birth. STÄMMLER (1915), on the other hand, maintains that no basophiles are ever seen in foetal hypophyses. When studying about 30 hypophyses from stillborn children or such as died during the neonatal period, the present author found a few basophile cells only in a few cases, the vast majority, however, showing absolute none. Even without a differential count, then, it should be permissible to assert that the hypophyses in the cases described above had an unconditionally pathological cellular composition.

As mentioned above, a placental lesion is an indispensable requisite for iso-immunisation. It is therefore very interesting to know that, in erythroblastosis, the placenta presents a pathological structure (HELLMAN & HERTIG). Under normal conditions, the syncytium cell layer of the placenta is the barrier permitting the passage of substances necessary to the life and growth of the foetus, but not letting through any red blood corpuscles. When this cell layer degenerates, as in erythroblastosis, the red blood corpuscles have the chance to pass from the foetus to the mother, thereby conducing to an Rh iso-immunisation — when, that is to say, the other conditions are favourable. Thus, this iso-immunisation is secondary to the placental lesion. However, the primary element in the disease cannot be the placental change which involves the foetal part of the organ, since it must be accepted that the mother is the bearer of the injurious factor causing the disease.

However, it must be noted that certain of the demonstrated disturbances of the endocrine functions seem to provide a possibility of explaining the erythroblastosis without assuming an Rh iso-immunisation. As TSCHERNE stated, an abnormally large oestrone production, whether in the placenta or in the maternal organism, may be followed by all the patho-anatomical changes in erythroblastosis; large doses of oestrone impair the haemopoiesis (cf. ARNOLD *et al.*, VÁRADY), activate the pituitary antidiuretic hormone with oedema as result, and may also induce the changes

in the endocrine organs. However, LIEBEGOTT and BENEKE attribute the oedema to hyperinsulinism.

Such a theory of a wholly hormonal genesis for erythroblastosis without the assumption of iso-immunisation nevertheless does not explain either the accumulation of cases within the blood group combination of mother Rh(—) — child Rh(+) or the customary finding of anti-Rh factor in the mother. Now, of course, the objection may be raised here that the only cases where iso-immunisation is conceivable is precisely in the blood group combination in point with a concurrent placental lesion enabling the red corpuscles to pass from foetus to mother. It should also be noted that the theory of an Rh iso-immunisation as main cause of erythroblastosis may easily acquire exaggerated importance if one gives way to the temptation of excluding cases which are otherwise similar, but where the regular blood group combination is not present. If the diagnosis of erythroblastosis is not made unless this combination is present and anti-Rh factor has been demonstrated in the mother, it is only surprising that the percentage for combination and anti-Rh alike is not 100 instead of 90 and 50—90 respectively. In any case, the clinical diagnosis of erythroblastosis seems to be difficult to make; mild degrees of hydrops may be readily overlooked by obstetricians, icterus gravis must sometimes be hard to distinguish from the physiological icterus neonatorum, and an anaemia during the neonatal period need not be a symptom of erythroblastosis. Incidentally, the patho-anatomical diagnosis may also be difficult, since all transitions exist between a massive extramedullary haemopoiesis and a total absence of the same, so that it is not easy to set the limit between what is pathological and what is physiological in this respect. Nor, plainly, is there any direct correlation between the degree of extramedullary haemopoiesis and the clinical intensity of the disease. The suspicion that there is an argument in a circle as regards Rh iso-immunisation as *theory* and *symptom* is borne out by an inspection of the case histories communicated by BROMAN. In a group of cases called »children with diseases resembling erythroblastosis» (author's italics), there are seven cases of hydrops foetalis, which were clearly not considered

erythroblastosis partly on account of atypical blood group combination and the fact that they were isolated occurrences in the family, partly because four of the cases were able to show endocrine disturbances which were in themselves sufficient to explain the course of the disease. That is to say, two of these cases showed a clinically verified and, in this connection, extremely interesting hypoglycaemia, in both cases without diabetes in the mother. In the third case »hormonal deficiency?» was recorded, in the fourth »chondrodystrophia + struma». It is most questionable whether this method of ruling out the diagnosis in the absence of serological conditions for Rh iso-immunisation, and in the presence of endocrine disturbances, is justified.

It is therefore likely that considerably more cases of erythroblastosis neither have the qualifications for nor show signs of an Rh iso-immunisation than would appear from the literature. That cases negative as regards Rh iso-immunisation are described at all is probably due to their having shown clinical and patho-anatomical symptoms of a kind to make the diagnosis inevitable.

But even if most of these cases with symptom pictures »resembling» erythroblastosis are included among the certain cases, there should nevertheless be a marked accumulation in the blood group combination of mother Rh(—) — child Rh(+), and a high per cent for the finding of anti-Rh factor in the mother. It should therefore be difficult to disregard Rh iso-immunisation when interpreting the clinical disease pictures in erythroblastosis, even if one is not inclined to accord it any genetic importance for the disease in its entirety.

The following explanation of the genesis of erythroblastosis foetalis should make it possible to reconcile the patho-anatomical picture and the clinical symptomatology, including Rh iso-immunisation. The *primary* element in the disease is an *endocrine dysfunction in the mother*, which induces a placental change and changes in the endocrine organs of the foetus (perhaps mainly via its hypophysis), with resulting dysfunctions according to the character of these changes. The literature's data point to an abnormally high production of oestrone or gonadotropic hormone

(these hormones can be thought to be formed both by the mother and in the placenta); as regards the progesterone state, nothing is known, but it is possible that this hormone, too, plays a part in this connection. Thus, the foetus is placed in an abnormal endocrine situation in utero. It doubtless owes survival during the foetal life partly to its great powers of adaptation to these successively increased hormone quantities, and partly to the fact that the abnormal quantities of hormone formed in the foetus's own changed endocrine organs are in large measure absorbed through the safety valve which the placenta can be taken to constitute. When, however, this valve is suddenly closed, at partus, the foetus is obliged to bear the brunt of its own abnormally large hormone quantities. The prognosis *quoad vitam* then depends on which hormonal functions are upset, and to what extent. Probably, the early death in hydrops foetalis is in many cases due to acute hyperinsulinism with hypoglycaemia. Another matter which is of unquestionably great importance is that, at delivery, the foetus is suddenly deprived of the abnormally large quantities of hormones which are formed in the placenta and in the maternal organism, and which it got accustomed to in utero. — In cases allowing for it — i. e. in the presence of the typical blood group combination of mother Rh(—) and child Rh(+) — the injured placenta's permeability by red corpuscles gives rise in more or less high percentage of the cases to an Rh iso-immunisation. The decomposition of the blood induced by the anti-Rh factor which is formed by the mother and transferred to the foetus, is compensated in greater or lesser measure by the haemopoiesis-stimulating effect set up by the slightly raised hyperoestronaemia (cf. FEUCHTINGER). When the child is separated from mother and placenta at birth, this stimulating effect is suddenly withheld, the decompensation of the blood remains uncompensated, and icterus gravis neonatorum sets in. If the intensified haemopoiesis in utero has not been able to keep level with the decomposition of the blood, the child is born with anaemia gravis neonatorum. This anaemia can also be explained by saying that the stimulating effect which the oestrone has in moderate concentration changes into an inhibiting effect when

the oestrone content exceeds a certain level — an explanation that does not need to take an Rh iso-immunisation into account.

It is obvious that if this theory is correct, Rh iso-immunisation plays a great part in the occurrence of icterus gravis and anaemia gravis, while it is not at all so important in hydrops foetalis. This also appears to a certain extent from BROMAN's material — 3 cases of »certain» erythroblastotic hydrops, 7 »rejected» cases.

As has been pointed out by a number of the modern authors on the subject, the occurrence of an Rh iso-immunisation is also particularly important in the therapy. That is to say, when giving blood transfusions, Rh(—) blood must be used — i. e. not blood of the same group as the recipient, who practically always belongs to the Rh(+) group; this is because the anti-Rh factor present in the child's blood rapidly haemolyzes administered Rh(+) blood corpuscles, whereas Rh(—) corpuscles resist this effect.

However, blood transfusions are to be considered a purely symptomatic therapy. On the theory of the disease's genesis advanced above, an administration of hormone would offer a more causal therapy. In this case oestrone should be tried in the first place (as has already been suggested by DE SNOO, who claimed to have obtained good results with it), though gonadotropic hormone (and possibly progesterone also) may repay a trial. These preparations should be given in large initial doses, with a subsequent successive decreasing of the dosage. Hydrops foetalis hardly ever provides occasion for any therapy, but if the foetus is born alive, it should be rapidly ascertained whether or not there is hypoglycaemia, in order to try raising the blood sugar value with glyucose and adrenaline as early as possible. When there is anaemia, blood transfusions should also be given, of course. In these cases, too, trials with oestrone and so on should be made, here probably in very large doses, since the hydrops cases are to be considered the most serious, and it can therefor be assumed that they were exposed to the most intensive dysincretion in utero.

It may be interesting to mention that fetuses of diabetic mothers often present the patho-anatomical picture of erythro-

blastosis (WHITE & HUNT). This tempts one to ask oneself whether various endocrine dysfunctions in the mother are not able to cause erythroblastosis — that is to say, it is not only a certain definite pathological condition in the mother that constitutes the pathogenesis of erythroblastosis foetalis. Intimately related as the functions of the different endocrine organs are, it is easy to suppose that an abnormal function in any one of them during pregnancy may set up that disturbance in the production of oestrone (gonadotropic hormone or progesterone) which in its turn induces the erythroblastotic changes in the foetus. This would then imply that the question of erythroblastosis has emerged from its previous narrow bounds, and has instead become a more generally endocrine problem.

A final word on the name of the disease. On the theory advanced here, the designations »erythroblastosis foetalis» and »morbus haemolyticus neonatorum» both refer to haematological participating phenomena in the disease pictures, and not to the fundamental cause of disease. If, as is not really necessary, a collective term is required for the three forms of manifestation, i.e. hydrops foetalis, icterus gravis and anaemia gravis neonatorum, it should refer to the genesis of the disease, the importance of the endocrine factors being in some way indicated.

Summary.

1. The earlier known changes in the endocrine organs in erythroblastosis foetalis, i.e. adrenocortical hyperplasia and insular hyperplasia in the pancreas, are supplemented by a pituitary change observed in two cases of hydrops foetalis and consisting of an increase in the basophile cells.

2. A critical study of the theory of an Rh iso-immunisation as the fundamental cause of erythroblastosis is considered to show that this theory is unable to provide an explanation either to the disturbances demonstrated in the endocrine organs and their functions, or to the fact that the dangerous symptoms do not set in until in association with or after partus. In any case, no

small number of cases lack the serological conditions for an Rh iso-immunisation.

3. A new theory is advanced, intended to explain the genesis of erythroblastosis as a primary endocrine dysfunction in the mother, which induces a placental lesion and changes within the foetal endocrine organs, resulting in its turn in endocrine disturbances; in many cases, especially in hydrops foetalis, these disturbances are thought to determine the issue. When the appropriate serological conditions are present, the placental lesion paves the way for an Rh iso-immunisation; this iso-immunisation is considered to influence the appearance of icterus gravis and anaemia gravis neonatorum.

4. On the basis of this theory, the author sketches the lines of a hormonal therapy in erythroblastosis foetalis.

References.

- ARNOLD, O., HAMPERI, H., HOLTZ, F., JUNKMAN, K. & MARX, H.: Arch. exp. Path. 186: 1, 1937. — BENEKE, E.: Zbl Path. 72: 401, 1939. — BROMAN, B.: Acta pædiatr. 31, suppl. II, 1944. — BURGER, K.: Kongressberichte Amsterdam 1938: 440 (cit. ZIGMOND). — BURNHAM, L.: Am. J. Obst. & Gynec. 42: 389, 1941. — DIAMOND, L., BLACKFAN, K. & BATY, J.: J. Pediatr. 1932, I: 269. — FEUCHTINGER, O.: Arch. exp. Path. 196: 644, 1940. — HELLMAN, L. & HERTIG, A.: Am. J. Path. 14: 111, 1938. — HERNBERGER, K.: Arch. Gynäk. 170: 287, 1940. — KRAUS, E.: Handb. d. spez. Path. Anat. VIII: 816, 1926. — LANGLEY, F. & STRATTON, F.: Lancet 1944 I: 145. — LEVINE, PH., KATZIN, E. & BURHAM, L.: J. A. M. A. 116: 825, 1941. — LIEBEGOTT, G.: Beitr. Path. 101: 319, 1938. — RACE, R., TAYLOR, G., CAPPELL, D. & MCFARLANE, M.: Brit. Med. J. 1943 II: 289. — STÄMMER, M.: Virch. Arch. 219: 226, 1915. — TSCHERNE, E.: Arch. Gynäk. 167: 489, 1938. — VON PALLOS, K.: Zbl Gynäk. 1939: 2352. — VÁRADY, M., Arch. Kinderheilk, 120: 104, 1940. — ZIGMOND, Z.: Bib Gynäk. 65: 1258, 1941.

FROM THE MEDICAL DEPARTMENT OF THE CHILDREN'S HOSPITAL,
GOTHENBURG. THEN ACTING HEAD: DR. GERT VON SYDOW.

Acute Benign Mononuclear Meningitis.¹

By

ERIK JACOBSSON, Stockholm.

Our knowledge of acute benign mononuclear meningitis is built upon the accumulated experiences of the past three to four decades, there having been hardly any possibility prior to that of distinguishing the non-bacterial from the bacterial meningitis. The first to report anything on this point was BABINSKI, who in 1907 wrote of a meningitis cerebrospinalis pseudoepidemica. Since then, and especially after the twenties, reports of these benign types of meningitis have been fairly frequent, so that by the present time there are contributions of this nature from the great majority of countries. Most of them, however, only describe a few single cases, large epidemics being but rarely mentioned. The first to submit this disease to a rather searching study and to contribute in no small degree to elucidating its terms and marking off its systematology was WALLGREN. At the Neurological Congress, 1924, on the basis of his own observations and analyses of previously reported cases, he described a morbid picture which he called Meningitis aseptica acuta or meningitis aseptica benigna. In the recent literature the term »acute aseptic meningitis» has been gradually superseded by the expression »acute benign mononuclear meningitis», chiefly because the term »aseptic» is no longer considered permissible for a state in which it has been considered more and more possible to trace the presence of a special pathogen in the form of some variety of virus or suchlike.

WALLGREN set up the following six points for the demarcation of this disease:

¹ Read in abbreviated form before the Gothenburg Society of Physicians, March, 1944.

- I. Acute onset with distinct meningitic symptoms.
- II. Meningitic changes in the cerebrospinal fluid, ranging from merely a slight increase of the mononuclear elements to a definite turbidity from leucocytes.
- III. Sterile fluid both in direct test and on culture.
- IV. Relatively short benign course without secondary neurological complications.
- V. Absence of demonstrable cause in the form of local affections (otitis, trauma, etc.) as well as in the form of a general infective disease (acute or chronic).
- VI. Absence of epidemiological relations to the known infective states producing meningitis: parotitis, poliomyelitis, encephalitis, etc.

As regards in particular the relations of the disease to poliomyelitis and encephalitis, these have been discussed by several authors. While some authors consider the mononuclear meningitis to be merely an abortive form of one or the other of the two diseases according to the different epidemiological conditions; others and probably the majority contend that it is a disease *sui generis*. The advocates of these views have put the very acute onset with high but gradually and often rather rapidly falling temperature in mononuclear meningitis in opposition to the so-called dromedary type of fever in poliomyelitis, viz. an acutely appearing and fairly high fever-peak (marking the forerunning general infection), later a rapidly falling temperature attended by a mild subfebrile state for a few days, thereupon another rise of temperature marked by a more protracted course and accompanied by the known more or less pronounced symptoms from the nervous system. On the other hand, a poliomyelitis may also set in acutely with signs of meningitis, and paresis of any outstanding degree need never be observed. With respect to the differentiation of acute mononuclear meningitis from encephalitis, the same difficulties present themselves here as in its discrimination from poliomyelitis. In the majority of the cases described in the literature paralytic as well as other symptoms indicative of an involvement of the nerve substance itself

are usually absent. On the other hand, most authors (WALLGREN, GUNTHER, etc.) give single cases with mild paresis, especially of the cranial nerves. Certain authors (LESNÉ and BOQUIEN, quot. by FANCONI) even assign a dual nature to the encephalitis, with all transitions between a meningitic and an encephalitic form.

In parotitis a biphasic course is also to be found as a rule, with a first phase marked by swelling of the parotids and a later phase of meningitic signs. Here too, however, there are cases described in which the meningitis has been the first and only symptom of disease and in which solely the relation to a parotitis epidemic in progress and a verified parotitic infection have enabled the diagnosis of parotitic meningitis to be definitely established.

Thus, if it cannot be settled with absolute certainty whether the acute mononuclear meningitis is an abortive form of poliomyelitis or encephalitis or of both, there are nevertheless some epidemiological as well as clinical facts which tend to show the independence of the disease. Certainly it seems in recent years to have been diagnosed more often than formerly, but doubtless it was as frequent in occurrence then but went under another name and was interpreted differently. The real pathogenic agent hardly seems to be definitely known as yet. In America ARMSTRONG and co-workers have succeeded in isolating an ultrafiltrable virus which produces severe reactions when injected into monkeys, though only intracerebrally. On the other hand, if this virus is injected subcutaneously, an immunization against intracerebral application is brought about. Now if serum from immune monkeys is mixed with the virus, the latter is no longer pathogenic when injected intracerebrally. The view that an infection is really concerned here is also afforded some support by the fact that it has been possible to demonstrate antibodies in patients, who were in the convalescent stage following an aseptic meningitis, though not in the first stages of the disease. By demonstrating the presence of antibodies in human serum these authors have come to the conclusion that the clinical unity »aseptic meningitis« has not a uniform etiology. Especially in

the age of childhood the Armstrong meningitis is thought to be rare, which is also confirmed by the experiments of FANCONI.

The acute lymphocytic form of meningitis occurs mainly sporadically, though occasionally it also appears in the form of small local epidemics, sometimes lasting a year or two. According to several observers there is an accumulation of cases in late summer and autumn, though individual authors have their maxima in the spring, while others find a fairly diffuse dissemination over the whole year. As a rule, no contact between the sufferers has been traced in the individual epidemics; only in a few cases have two siblings or two class-mates been attacked. The victims are usually children and young people, but there are reports of cases from two months of age to 76 years. There are also epidemics to which only adults have fallen victim (SCHNEIDER).

As regards the symptomatology, this seems to be rather similar in cases described by different authors. After sometimes mild prodromes the symptoms as a rule set in rather acutely with headache, frequently neckache and backache, vomitings and fever as well as often fatigue. The temperature is mostly high, the headache usually very intense, the vomitings may stand out more or less prominently. Sometimes the sensorium is somewhat dimmed, often it is strikingly clear and consciousness is retained. Ocular symptoms are occasionally described, and sometimes abdominal pains. Objectively, besides a more or less pronounced neck rigidity and Kernig's sign, there are found no or only quite insignificant neurological symptoms, such as anisocoria, pupillary sluggishness, mild strabismus, i. e. chiefly cranial-nerve symptoms. Lumber puncture shows a moderately increased pressure and usually a clear, at times a turbid, fluid. The number of cells in the fluid is raised, though usually rather moderately and seldom up to 1000, only very rarely above that. The majority of the cells consist of lymphocytes or mononuclear cells, as a rule at least about 60—70 %. In the most acute stage, however, there is sometimes seen a predominance of leucocytes, a picture, however, that is rapidly succeeded by a predominating lymphocytic one. The protein values of the fluid are often

slightly raised, often normal. The fluid is sterile. Sometimes the white corpuscle picture shows a leucocytosis, sometimes normal values. The sedimentation rate is variable and as a rule not especially high. A benign course is followed, and all — at any rate subjective — symptoms have usually vanished after 5—8 days, though the fluid often shows mild changes for still some time.

The therapy need not be other than symptomatic, although of late years various sulphonamide derivatives have come into use, whether with greater success than when nothing was done may be open to doubt. According to some workers, lumbar puncture has a good therapeutic effect. A case here and there is described that has led to death. In one of these, autopsy disclosed that not only the meninges but also the brain was studded with mainly perivascular lymphocytic infiltrations.

A comparison and follow-up examination of the cases of acute aseptic meningitis treated at the Gothenburg Children's Hospital during the years 1922—28 was carried out in 1929 by GUNTHER, who found altogether 13 cases during this period. He considered that in the majority of cases he could trace a certain epidemiological connection with poliomyelitis. This finding, in conjunction with the agreement in the clinical picture between these meningitis cases and poliomyelitic meningitis, induced him, at least in a number of cases, to consider it probable that abortive forms of poliomyelitis were involved here.

Since Gunther's investigation and up to the present time a further 12 meningitis cases belonging to this category have been treated at the Children's Hospital, three of which during the years 1932—33, three during 1938—39, and six after 1942. A brief summary of these cases follows.

Case I. No. 1137/32. Boy, aged 3 mths, admitted Dec. 5. Drowsy and unwell on night preceding day of adm., would not eat. Vomited rather much. *On exam.:* Affected general condition. Good colour. Large fontanel depressed. Lumbar puncture: Fluid runs extremely slowly, is not perfectly clear. Initial pressure not measurable. Pandy +. 400 cells, practically all mononuclears. Mantoux neg. to 1 mg. *Dec. 10:* Gen. cond. better. Tolerably good appetite. Large fontanel still depressed. No

neck stiffness. Has squinted at times, less past few days. Sedim. rate of R. W. C., 5. Hb. 66 %. W. B. C. 7500. *Dec. 14:* Lumbar p. Initial pressure 500 mm. H₂O (screams). Clear fluid. Pandy, trace. Cells: 5, only lymphocytes, and 370 R. B. C. per cmm., some shaped like a spiked club. *Dec. 16:* Gen. cond. good. No paresis. Good appetite. *Dec. 27:* Home. Therapy: Nil.

Case II. No. 570/33. Boy, 14 yrs. Adm. May 27. Fell ill one week before entry with fever and vomitings. In bed a day or two but was up later until May 25, the whole time mildly subfebrile. May 25: Temp. 39°. May 26, vomited. Since then headache at times, but no vomiting. *On exam.:* Unaffected. Slightly pale. Fain sign of neck stiffness. Kernig very weakly pos. Sedim. rate 6. Hb. 86 %. Mantoux pos. to 0.1 mg. Lumbar puncture: Initial pr. 150 mm. H₂O. Queckenstedt normal. Pandy +. Nonne weakly pos. Ross-Jones weakly pos. 66 cells, 88 % of which lymphocytes. *May 29:* Unaffected. No headache or vomitings. Slight signs of neck stiffness. Kernig pos. 45°. *May 31:* Kernig 60°. *June 3:* Home for further rest in bed. Therapy (from 6th day): Urotropin 0.5 gm., 3 times daily for 3 days.

Case III. No. 841/33. Boy, 7 yrs. Adm. Aug. 21. Onset in the morning of Aug. 19 with fatigue, pain in back and general malaise and vomited once. Night before adm. cried in his sleep and was delirious. *On exam.:* Unaffected. Complains of back pains. Distinct neck stiffness. Laségue pos. 70°—80°. Both patellar and Achilles reflexes, though weak. Babinski neg. Sedim. rate 6. Hb. 93 %. W. B. C. 6200. Mantoux neg. to 3 mg. Lumbar puncture: Initial pr. 150 mm. H₂O. Water-clear fluid. Pandy +. Nonne weakly pos. Ross-Jones weakly pos. 38 cells, chiefly mononuclears. *Aug. 24:* No headache. Lively and gay. A little neck stiffness. Laségue 80°. *Aug. 26:* Home, but some difficulty in sitting up. Therapy: Nil.

Case IV. No. 1055/38. Boy, 9½ yrs. Adm. Oct. 10. Fell ill Oct. 28 with headache, next day temperature up to 40°. Subsequently had very severe headache and vomited on one occasion. Slept badly and was delirious during night preceding entry. *On exam.:* Affected gen. cond. High colour. Not quite lucid, nor fully oriented, but answers on being addressed. Distinct stiffness of neck and back. Laségue pos., bilat. 50°—60°. Reflex normal. Fundi oculi unaltered. Sedim. rate 26. Hb. 85 %. Hamburger's the ointment test, pos. Lumbar p.: Init. pr. 230 H₂O. Queckenstedt and movements normal. 25—30 cc. of moderately turbid fluid tapped. Pandy ++++. Cells 2140/emmm., 75 % of which lymphocytes. No bacteria. Culture: No growth. W. R. neg. *Oct. 31:* More lucid, less affected. Lumbar p.: Init. pr. 200 mm. 25 cc. of slightly

turbid fluid tapped. Pandey +. Nonne +. Cells 990, 60 % of which lymphocytes. No bact. Culture: No growth. Nov. 2, lumbar p.: Init. pr. Sedim. rate 25. Hb. 78 %. Nov. 8: Gradually more lucid. Slight headache. Slight neck stiffness. Nov. 12, lumbar p.: Init. pr. 110 mm. Water-clear fluid. Pandey —. Nonne —. Cells: 6 lymphocytes. Nov. 18: Sedim. rate 8. Hb. 77 %. Home. Therapy: Sulphonamide 0.5 gm. \times 4 for 4 days, 0.25 gm. \times 4 for 5 days.

Case V. No. 1045/39. Boy, 11 $\frac{1}{2}$ years. Adm. Aug. 31. Attended here earlier for tb. pulm. prim. Fell ill one week before adm. with fatigue, but went to school for two days. Five days before adm. abrupt rise of temp. to 40°, then lay with fever 38°, 39.2° (3 times). Complained of headache and wanted to sleep much. Very drowsy day of adm. *On exam.*: Small, rather lean, with distinct lip cyanosis. Slightly disoriented, dimming, but gives adequate answers. Moderately severe headache. Manifest neck stiffness. Pos. Kernig, 30°. Weak patellar reflex. Babinski neg. bilat. Pupils normal. Sedim. rate 27 mm/hour. Hb. 63 %. Mantoux neg. to 1.0 mg. Lumbar puncture: Init pr. 190. Queckenstedt normal. Slightly opalescent fluid. Nonne ++. Pandey ++. Cells 620 per cmm., 67 % of them lymphocytes. W.R. neg. Culture of punctate: No growth. Sept. 4, lumbar p.: Water-clear fluid. Pandey, faint trace. Nonne neg. 11 cells, mainly lymphocytes. Culture: No growth. Sept. 5: Has been steadily improving. Now everything normal. No neck rigidity. Pos. Kernig, 60–70°. Sedim. rate 19 mm. Hb. 77 %. Oct. 4, lumbar p.: Init. pr. 160 mm. Clear fluid. Pandey —. Nonne —. Cells, 3. Sed. rate 13 mm. Hb. 78 %. Became afebrile on second day after entry. Therapy: Nil. Home Oct. 7.

Case VI. No 1255/39. Boy, 15 years. Adm. Nov. 3. Onset Nov. 1 with headache and vomitings; since then in bed. Vomited the whole time. Slept badly, been quite lucid. The headache has increased in severity. *On exam.*: Somewhat affected. Good colour. Urticarial-like exanthema on trunk and extremities. Quite lucid. Complains of headache. Neck stiffness. Laségue pos., 30–40°. Normal reflexes. No paresis. Normal ocular fundi. Sedim. rate 22 mm. Hb. 85 %. W.B.C. 18 400. Mantoux neg. to 1.0 mg. Lumbar puncture: Water-clear fluid runs out at normal rate of drip. Pandey +. Nonne weakly pos. Cells, 173 per cmm., 90 % of which lymphocytes. Culture: No growth. Nov. 9: No vomiting since day after entry. His headache has successively improved; gone last two days. Neck stiffness gone. Laségue neg. Nov. 13: Sed. rate 13. Hb. 84 %. Nov. 25, lumbar p.: Init. pr. 160 mm. Clear fluid. Pandey and Nonne both neg. Cells: 5 white. Culture: No growth. Afebrile on 5th day after adm. Therapy: Septipulmon, sedatives, salicylic-acid preparations. Nov. 30: Home.

Case VII. No 734/42. Baby girl, 8 months. Adm. May 10. Acute onset May 5 with vomiting. Since then loss of appetite, has wanted to sleep. No coryza or cough. Her temp. was taken on May 9 and was then 39.8° . Lay dozing most of that day. *May 10:* Several spastic attacks in arms and legs. *On exam.:* Gen. cond. greatly affected. Dyspnoeic. Lies with conjugate deviation to the right and clonic spasms in arms and legs. Reacts to pricks. No neck rigidity. Neg. Kernig. Large fontanel one finger-breadth, not tense. Craniotabes pos. Thoracic deformities pos. Epiphyseal enlargements pos. Patellar reflex pos. Normal pupils. Sedim. rate 18 mm. Hb. 84 %. W. B. C. 20 200. Mantoux neg. to 1.0 mg. Nervous response to electrical stimulation not augmented. Blood: Calcium 10.4; phosphorus 3.3. Repeated attacks of spasm in hospital in the course of the morning. Lumbar puncture: Init. pr. 400 mm. Free movements. 10 cc. of clear fluid with slight yellow tinge. Pandy ++. Nonne +. Cells 79, 90 % of which mononuclears. *May 11:* Sulphathiazol instituted in double dosage according to pneumonia scheme. On May 11 at 9 p.m. and on May 12 at 8 a.m. small twitchings in arms and legs. *May 13:* Nystagmus, which has not been observed since. *May 16:* Improved. Seems to stare. General condition improved. No neck stiffness. *May 21.* Uneasy preceding day, calmer today. No neck rigidity. Large fontanel normal. Sedim. rate 16 mm. Hb. 60 %. Lumbar p.: Init. pr. not measurable. After tapping 45 cc. of slightly bright straw-yellow fluid the pressure was 450 mm. Queckenstedt normal. Pandy ++. Nonne ++. Cells, 10 white, 1 130 red, shaped like spiked club. Culture: No Growth. *May 22:* More alert again. Follows movements with her eyes. Gets angry and cries on being touched. Conjugate deviation off and on. No neck stiffness. At times a suggestion of clonus in the arms. *May 29:* Bright and alert. Follows movements with her gaze. Clutches at toys and looks at them. Makes attempts to prop herself up. Possibly a slight lag of the right facialis. Sedim. rate 19 mm. Hb. 68 %. *June 1:* No paresis of the facialis. Bright and alert. Home. Given sulphathiazol in double dosage for 8 days, then the usual pneumonia dose for one week. W. B. C. 14 000—16 000 all the time, towards the end 10 000. Not afebrile until 14 days later. *Diagnosis:* Meningo-encephalitis + Rachitis + Pharyngitis + Debilitas psychica?

Case VIII. No. 45/43. Girl, aged 8 months. Adm. Dec. 26, 1942. Drooping and whining on Dec. 24, next day appetite worse, in the afternoon coryza and plugging up of the nose. At 8 p.m. solitary twitchings in one hand and the arm; passed off rapidly. At 10 p.m. small twitchings began here and there, and the child did not seem to be fully conscious. Brought here at 12 : 30 in the night. *On exam.:* Rather pale with small and quite anomalous twitchings of all the muscles of the

body. Conjugate deviation to right. Large fontanel not tense, no neck stiffness. Reddened pharynx. Pupils react to light, though sluggishly. Normal reflexes. Normal responses to electrical stimulation. Lumbar puncture: Slight white turbidity of fluid, which drips at rapid rate. Init. pr. 500 num. Pandey ++. Nonne +. Cells 5190 per cmm., 90 % of which polynuclears. Sedim. rate 30 mm. Hb. 71 %. W. B. C. 46 600. Mantoux neg. to 0.1 mg. Next night minor spasms in left side, but subsequently no spasms. Dec. 29: Gen. condition much better. Follows movements with her eyes. Dec. 31: Not moved left arm and leg since yesterday, increased tonus in these. Jan. 4: Moves left arm more today and raises left leg a little; yesterday a rise of temp., otherwise unaffected. Lumbar p.: Haemorrhage from puncture. Pandey +. Nonne +. Cells 8500 R. B. C. (club-shaped); 67 W. B. C. per cmm., mainly lymphocytes. Jan. 7: Equal movements now of extremities on both sides. Jan. 9: Dyspepsia. Jan. 29: In excellent form. Lively and cheerful; playful. Grasps better with left hand, though not quite as ordinarily, still some rigidity there. Home. Therapy: Sulphathiazol for 11 days.

Case IX. No. 718/43. Girl, aged 5 months. Adm. May 10. Cough, coryza and fever for last week. Afebrile day before adm., 41° on day of adm. On exam.: Gen. cond. affected, pale and pulled down, dirty-grey tinge. Large fontanel two finger-breadths; if anything slightly depressed, but tense at the bottom. Lies with head bent backwards and resists forward bending. Moderate pharyngitis. Lumbar puncture: Init. pr. seems unincreased. 10 cc. of water-clear fluid tapped. Pandey, weak trace. Nonne neg. Cells, 30 white per cmm., chiefly lymphocytes. Culture: No growth. Mantoux neg. to 1 mg. Sedim. rate 28 mm/hr. Hb. 81 %. W. B. C. 43 800. May 14: Much improved gen. cond. Apyretic after 24 hours of sulphathiazol treatment. May 20: Lively and laughing. Good gen. cond. No neck stiffness. Home.

Case X. No. 112/44. Girl, aged 11½ years. Adm. Jan. 3. Taken ill on night preceding Jan. 2 with fever and vomitings. Jan. 3: Temp. 39.9°. Complained of aching pain in head and stomach, had neckache even when lying. On exam.: Gen. cond. fairly unaffected. Lucid. Moderate headache. Sensation of numbness in right hand. Moderate neck stiffness, suggestion of back stiffness. Laségue pos. at 70° bilat. Patellar and Achilles reflexes bilat. pos., energetic and equal. Normal abdominal reflex. Babinski and Oppenheim: right neg., left pos.? No other neurological symptoms. Sedim. rate 7 mm/hr. Hb. 81 %. Mantoux neg. to 1 mg. Jan. 4: Achilles reflex not definitely elicited, even at *lege artis* tests. Babinski on both sides dubious (+ ?). Oppenheim, same findings. Lumbar puncture: Init. pr. 180 mm. 10 cc. of slightly turbid and very faintly rose-pink fluid tapped. Pandey +.

Nonne neg. 415 W.B.C., almost only lymphocytes, and 1 600 R.B.C. per emm. Culture: No growth. *Jan. 7*: No headache. Still marked neck rigidity ever since previous lumbar p. Babinski and Oppenheim are today pos. Patellar and Ach. reflexes bilat. pos. and energetic. Nothing neurological in other respects. *Jan. 10*: Feels well. No headache. Neck stiffness as before. Laségue and Kernig pos. 30—45° bilat. Arm reflexes normal as before. Patellar and Ach. as before. Babinski bilat. dubious; if anything, neg. Oppenheim neg. *Jan. 17*: L.P.: Init. pr. 250 mm. Clear colourless fluid. Pandey, trace. Nonne neg. Cells, 19 white per emm. *Jan. 24*: Neurologically as before. *Febr. 2*: Lively. No headache. Babinski and Oppenheim, left dubious, right neg. Sed. rate: 2 mm/hr. Hb. 76 %. *Therapy*: Sulphatiazol with freedom from fever on 5th day. Controlled *Febr. 20* as outpat.: Everything normal. Bab. and Oppenh. neg.

Case XI. No. 136/44. Boy, aged 7 years. Brother of case X. Adm. Jan. 8. Onset Jan. 7 with fever, 38.7°, shiverings, vomitings and severe headache. Been drowsy and vacuous yesterday and today, though not entirely insensible. Vomited repeatedly. On exam.: Fairly unaffected gen. cond. Admits headache. Quite lucid. Rather lively. Tonsillopharyngitis. Moderate neck stiffness. Laségue pos. 70°. Neurologically nothing abnormal. Lumbar p.: Init. pr. 400 mm. Fluid considerably blood-stained (puncture haemorrhage). Pandey + + +. Nonne + +. Cells 19 600 W.B.C. per emm., 90 % of which lymphocytes. R.B.C. 780 000 per emm. No growth on culture. Mantoux neg. 1 mg. Sed. rate 8 mm. Hb. 75 %. W.B.C. 6 700. *Jan. 12*: Feels well. No headache. Neurologically no change. L.P.: Init. pr. 310 mm. Slightly turbid colourless fluid. Pandey +. Nonne weakly +. Cells 358 W.B.C. per emm. Culture: No growth. *Jan. 18*: Feels well. No subjective symptoms now. Neurologically nothing abnormal. No neck stiffness. L.P.: Init. pr. 150 mm. Cells 19 W.B.C. per emm. Pandey neg. Nonne neg. *Febr. 5*: Home entirely symptomless. Sedim. rate 4 mm. Hb. 76 %. *Therapy*: Sulphatiazol with apyrexia on 5th day.

Case XII. No. 154/44. Girl, aged 1 year. Adm. Jan. 10. Taken ill on Jan. 7 in evening with 39°, subsequently having about 40° all the time. On admission day drowsy and stiff in back. A squint persisting for past half year had increased during the day. Had not vomited. No spasms. On exam.: Gen. cond. affected. Lies drowsy and responds badly to simple tests. Her face has a tense appearance. Marked neck stiffness. Neurologically normal in other respects. Moderate pharyngitis. Lumbar puncture: Init. pr. 450 mm. (Child quite calm.) Queckenstedt normal. Pandey +. Nonne +. Cells 4 080 W.B.C. per emm., chiefly lymphocytes. Cobweb clot. Culture: No growth. Sedim. rate 34 mm/hr.

Hb. 68 %. W.B.C. 10 100. Lumbar puncture. *Jan. 12*: Init. pr. 250 mm. Fluid slightly less turbid than before. At beginning and end slightly blood-stained. Pandey +. Nonne weakly +. Cells 288 W.B.C. per cmm. and 420 R.B.C. No growth on culture. *Jan. 18*: Now lively and well. Moves freely in bed. Interested in surroundings. Follows what happens. The strabismus continues as before. (Does not seem to move the eyes over laterally, especially left eye, though also to some extent right eye.) Neurologically nothing abnormal. *Jan. 20*, lumbar p.: Init. pr. below 180 mm. Clear colourless fluid. Pandey, trace. Nonne neg. Cells 21 W.B.C. per cmm. No growth on culture. *Febr. 1*, lumbar p.: Init. pr. 210 mm. Clear colourless fluid. Pandey and Nonne neg. 4 cells per cmm. Strabismus as before. *Febr. 8*: Seems now to move eyes normally over to both sides. All eye movements now quite free. Only squints now and then. Lively and charming. But screams and makes a great fuss on being examined. No pareses or other neurological symptoms. Sedim. rate 7 mm. Hb. 78 %. *Febr. 10*, home. *Therapy*: Sulphathiazol, under which gradual decline of temperature in the course of the first ten days.

All of these cases had a typical onset and a typical course, approximately as was described earlier. Apart from neck rigidity and more or less sensorial impairment there were no neurological symptoms, except in three cases. Two of these three were infant girls, aged 8 months, who, in connexion with the onset and during the immediately following 24 hours, had repeated attacks of spasm with clonic twitchings in the whole body, especially the arms and legs — symptoms that not so uncommonly attend an acutely onsetting fever in young children. Five days after admission, one of these two cases presented a paresis with increased rigidity in the left arm and leg. This had almost vanished on discharge of the patient after five weeks' hospital care, and after another two months was entirely absent at a control examination then undertaken. The third case, a girl, aged one year, had on entry a left-sided abducens paresis, which, although only very slight, was reported to have already been present earlier. The strabismus, that had thus arisen, disappeared in the course of the subsequent period of observation. So far as could be judged, all three patients were of normal development and psyche on leaving the hospital. Another case, an 11-years-old girl, exhibited unmistakable signs of progressive reflex disturbances during the first 24 hours, which

rapidly disappeared in the course of a couple of days. No paresis, however, could be observed in this case. This last-mentioned patient fell ill on Jan. 2, 1944, and exactly five days later, Jan. 7, her brother was also taken ill with exactly the same symptoms.

The fluid findings in these 12 cases are given in Table I. The only really remarkable feature presented by these, compared with Gunther's collection, is the high number of cells in the lumbar fluid of several cases. Gunther had three cases with respectively 700, 400, and 630 cells, the rest showing fewer than 200 cells per cubic millimetre. A possible explanation of the high number of cells in my material is the present-day tendency to place children as early as possible under medical treatment, the result being that cases are sent at an early stage to the hospital, where there are better facilities for determining any at the beginning of the disease obviously present powerful increase in cells than in later stages (Cf. Table I, Cases IV and XI). The usually very rapid regression of clinical symptoms as well as the fluid findings also argue in this direction.

A collection of all the cases of acute mononuclear meningitis treated at the Children's Hospital from the year 1922 up to the present time is given in Tables II—IV. It will be seen from these that although this disease occurs with a few cases amassed during certain years it does not on that account give rise to any outstanding epidemics. No indubitable connexion between the different cases during the respective years is observable. Exceptions from this are the two siblings (Cases X and XI), who were taken ill with an interval of five days. There seems to be no special age of predilection. Respecting the seasonal incidence of the cases, it may be said that the majority seem to occur during the autumn months — the three cases falling to January all occurred in 1944 and had their onset during the first week of January.

In this connexion it is of interest to note that in the Medical Department of Sahlgren's Hospital, Gothenburg, a certain accumulation of mononuclear meningitis cases has also been observed at roughly the same point of time as at the Children's Hospital. Thus, during the autumn of 1943, altogether four cases were

Table 1.
Cerebrospinal fluid findings.

Case	Date	Pressure in mm.	Appearance	Pandy	Nonne	Number of cells	Mono- nuclears	Poly- nuclears	Comment
I	5.12.32 14.12.32	? 500	slightly turbid clear	+ trace		400 5	almost all all		screams
III	27. 6. 33	150		+	weakly +	66	88 %		
II	21. 8. 33	150	clear	+	weakly +	38	majority		
IV	30.10.38 31.10.38 2.11.38 12.11.38	230 200 180 110	some turbid slightly turbid clear clear	++ ++ trace —	+ + — —	2140 990 51 6	76 % 60 % 57 % all		
V	31. 8. 39 11. 9. 39 4.10.39	190 160	slightly turbid clear clear	++ weakly + —	+ — —	620 11 3	67 % majority		
VI	3.11.39 25.11.39	160	clear clear	+ —	weakly + —	173 5	90 %		haemorrhage with 1 130 R.B.C./cmm.
VIII	26.12.42 4. 1. 43	500	slightly turbid slightly blood-stained	++ ++	+ +	5190 67	majority	90 %	8 500 R.B.C./cmm.
IX	10. 5. 43	not increased	clear	weakly +	—	30	majority		1 600 R.B.C./cmm.
X	4. 1. 44 7. 1. 44 17. 1. 44	180 240 250	slightly turbid clear clear	+ trace trace	— — —	415 294 10	majority majority		Punction haemorrhage: 780 000 R.B.C./cmm. 6 700 W.B.C./cmm.
XI	8. 1. 44 12. 1. 44 20. 1. 44	400 310 150	slightly turbid clear	++ ++ —	+ weakly + —	19600 358 19	90 % majority		fluid sugar 0.04 % cobweb clot. 420 R.B.C./cmm.
XII	10. 1. 44 12. 1. 44 20. 1. 44 1. 2. 44	450 250 180 210	turbid slightly blood-stained clear clear	+ + trace —	+ weakly + — —	4080 288 21 4	majority majority		

Distribution of the material by year of onset, age at onset and month of onset.

Table II.

Year	Number
1922	2
1923	1
1924	—
1925	5
1926	—
1927	4
1928	1
1929	—
1930	—
1931	—
1932	1
1933	2
1934	—
1935	—
1936	—
1937	—
1938	1
1939	2
1940	—
1941	—
1942	2
1943	1
1944	3

Table III.

Age	Number
0—1	5
1—2	1
2—3	—
3—4	1
4—5	1
5—6	2
6—7	1
7—8	3
8—9	1
9—10	3
10—11	—
11—12	4
12—13	—
13—14	1
14—15	1
15—16	1

Table IV.

Month of Onset	Number
Jan.	3
Febr.	—
March	—
April	2
May	4
June	—
July	—
Aug.	6
Sept.	1
Oct.	5
Nov.	2
Dec.	2

admitted there on the following dates: 24/9, 3/11, 20/11 and 22/12. I have been unable to find any other connexion between these cases and those of mine under review here. It was stated that among the Sahlgrenska adult cases there was a striking discrepancy between the fairly mild subjective discomfort and the much accentuated objective symptoms, especially as regards the fluid findings.

In order to form some idea of any relations this disease might have to poliomyelitis I have compared month by month all the cases of the respective diseases that have occurred since 1929.

Table V.

P = poliomyelitis. M = mononuclear meningitis.

	1929		1930		1931		1932		1933		1934		1935		1936		1937		1938		1939		1940		1941		1942		1943	
	P	M	P	M	P	M	P	M	P	M	P	M	P	M	P	M	P	M	P	M	P	M	P	M	P	M	P	M	P	M
Jan.							5				1								1											
Febr.																														
March			1																											
April									1						1		2				1						1			
May	1		2																											
June			3				1						1		1		3						2							1
July			2		1		7		3		1		1		12								1						3	
Aug.					1		17		1		5		5		20						1				3			1		
Sept.					1		2		2		59		2		17		5		2				2		2		2		1	
Oct.	1				4		5		1		32				11		1		1				1		1		1		16	
Nov.					3		1		1		29				3		1		1									10		
Dec.					1						2				2												1		3	
	3	—	8	—	11	—	38	1	8	2	129	—	9	—	67	—	12	—	5	1	1	2	—	—	9	—	3	2	34	1

and have found no agreement whatever (Table V). At the times at which poliomyelitis showed the most cases not a single case of mononuclear meningitis was diagnosed at the Children's Hospital, and this circumstance was especially noticeable for the years 1934 and 1936, when the wide-spread epidemics of poliomyelitis were raging in Gothenburg, no case of mononuclear meningitis being attended at the Gothenburg Children's Hospital from September 1933 to May 1938. On the other hand, it must be admitted that during poliomyelitis periods there is a tendency to consider all cases of meningitis as poliomyelitis or as abortive forms of this disease, even if the lumbar fluid shows mononuclear cells from the beginning. Hence the result of the comparison constitutes no proof in either direction. A similar comparison of the single cases of encephalitis epidemica that were diagnosed in Gothenburg during these years has likewise given no support whatever for any connexion between the two diseases.

During the months of November and December, 1943, as well as January, 1944, we had at this hospital five cases which we characterized as encephalitis. All the cases except one presented only minor neurological symptoms, e. g. very mild and transient paresis, in one case only headache, no other signs of meningitis occurring and the fluid finding being trivial: Pandy and Nonne were negative and the cells numbered respectively 2, 2, 5, 9, and 12. Naturally enough, the possibility has been suggested that one and the same pathogen was responsible for these two cases of encephalitis and for the three cases of mononuclear meningitis that occurred this year, this causative agent manifesting itself differently in different ways. Although this possibility cannot perhaps be definitely ruled out, no reasonably reliable support for such a state of things can be obtained. Four of the encephalitis cases fell ill during November and December, only one in the beginning of January and about ten days after the last case of mononuclear meningitis entered the hospital.

A study of the situation of the dwellings in the different cases showed that four of these cases of encephalitis had their homes in Hisingen, the fifth in Majorna, while all the four cases of mononuclear meningitis in children occurring during the past

year had their homes in Majorna (all the cases mentioned of mononuclear meningitis in adults had their homes situated in other parts of the town of Gothenburg, widely separated from each other). Between Majorna and Hisingen there is certainly a rather lively communication by ferry across the Göta älv, which separates the parts of the town, but the connexion between these cases does not seem to extend further. Nor has it been possible to educe any mutual connexion in other respects.

Summary.

Following a brief review of our present knowledge of acute benign mononuclear meningitis an account is given of 25 cases treated at the Gothenburg Children's Hospital since 1922 and a brief summary is appended of the case histories for the cases reported during the past 15 years. (For cases before 1929 reference may be made to Gunther's work.) The relations of the disease to especially poliomyelitis and encephalitis are discussed, it being claimed that no absolutely certain connexion between them has hitherto been demonstrated. The experiences gained from the present material likewise give no reliable support for such a connexion. The disease is not characterized by any specific sex- or age-distribution. Nor is the accumulation of cases in the autumn or spring cited by some authors confirmed by this material, which is distributed fairly uniformly over the whole year. As a rule, the course of the disease is very rapid and benign, both in respect of subjective and objective symptoms. There is no specific therapy, and nor is any necessary. Sulphathiazol and similar preparations can no doubt be avoided as a rule without being missed. The disease does not give rise to any future detriment in spite of the presence of minor symptoms of suppression in some cases.

References.

DUMMER, *JAMA* 108, 637, 1937. — ECKSTEIN, HOTTINGER & SCHLEUSING, *Ztschr. klin. Med.* 118, 911, 1931. — FANCONI, *Erg. d. Inn. Med. u. Kindhk.* 57, 399, 1939. (Contains an exhaustive bibliography.) — GUNTHER, *Jahrb. Kinderhk.* 128, 127, 1930. — SCHILLING, E., u. ZEUMER, G., *Med. Woch.* 1939. — VIETS & WARREN, *JAMA* 108, 357, 1937.

Allergic purpura with hypoprothrombinemia.

By

ARNE NJÅ.

In 1939 SEIDLMEYER described some cases of purpura in children, showing several common characteristic features, and presenting a sufficiently uniform clinical course to justify their grouping under a special type of purpura diseases: Die frühinfantile, postinfektiöse Kokarden-Purpura.

The affected children were of the age of seven months to $2\frac{3}{4}$ years. The disease occurred in connection with an infection, most often catarrhal inflammation of the upper respiratory passages, once also in connection with tuberculosis (tuberculous infection of the hilus glands). After one to several weeks of disease an exanthema erupted. Its primary lesion was an urtica or a papule, the size of a lentil or a pea, in which secondarily a central hemorrhage appeared, spreading in the surface. Thus bright red spots appeared, the size of a threepence to a shilling, which were slightly elevated above the surrounding skin. In the center a plain papule persisted, with a white anemic zone in the periphery. At this stage the lesions looked like cockades. Occasionally the hemorrhages increased in size up to that of a child's hand.

These lesions came in greater or lesser numbers, almost entirely symmetrically. The favourite sites were the extensor surfaces of the extremities and the seat, often also the face, particularly the cheeks. The trunk as a rule was free. In one case only there was a slight hemorrhage also from the mucous membranes (hematuria). During the disease attacks of urticaria often broke out, partly with

and partly without hemorrhages. A further characteristic feature of the disease was the tendency to edema, with edemata either around the hemorrhages or independent of these, particularly frequently on the back of the hands and the feet and in the face. In some cases there was a single outbreak of hemorrhage, in other cases new outbreaks came after an interval of one to several days. The hemorrhages receded after one or two weeks. SEIDLMAYER never saw a relapse under new grippe infections. In contrast to the SCHÖNLEIN-HENNOCH purpura no joint symptoms occurred, nor any colic pain, and there was no blood in the stools in any case, nor had any of the patients hemorrhagic nephritis. The blood findings presented no characteristic features. The platelets as a rule were found in normal numbers, but in some cases their number was temporarily reduced, at times considerably reduced. The bleeding time was normal, and the clot retraction was not delayed. The clotting time has only been examined in five cases. In three cases it was found to be normal, in one patient slightly prolonged (clotting beginning after 5 minutes, complete after 20 minutes), and in one patient it was considerably prolonged, viz. 55 minutes. The prothrombin time does not seem to have been examined in any of the SEIDLMAYER cases.

OPITZ has seen some patients with a similar clinical picture, and he agrees with SEIDLMAYER's terminology. He emphasizes the pronounced tendency of edema in the face and on the head. Further he has considered it striking that in nearly all the patients hemorrhages occurred in the auricular conchae. According to his experience hemorrhages from the mucous membranes are not infrequent, as in his five cases he has observed hemorrhages from the conjunctiva, the kidneys, the intestines, and in the cavity of the mouth. SEIDLMAYER maintains that weeks of infection precede the hemorrhages. This is not the case, however, in all the cases of OPITZ, in which the previous infectious period sometimes was shorter. In one patient the disease suddenly broke through a perfectly good health. As a rule the patients were feverish for one or two weeks. GLANZMANN also mentions SEIDLMAYER's »cockade purpura», but he thinks that the cases ought rather to be included in the same group as the purpura fulminans. From Scandinavian

quarters cases of this type are not known to have been previously described.

In the University Clinic, Department of Pediatrics, we recently saw a case, which falls closely into line with SEIDLMAYER's »Frühinfantile Kokarden-Purpura.»

The case concerns a one year old boy, who was admitted into the department on April 27th 1944. He was born on time and was a breast-fed child. There was no information as to allergic lesions in the family. Two months before admission he had pseudo-croup, and four days before admission he got suddenly ill from dysphagia, fever and hemorrhages in the skin. The mother had the impression that he had pain when she touched him. Due to a coated throat he was first admitted into The Epidemic Department as suspected of diphtheria. Extensive skin hemorrhages on the extremities and in the face were recorded. On April 24th, the day after the boy entered The Epidemic Department, the following addition to the journal is made: The skin hemorrhages have greatly increased since yesterday. On both the lower arms there are confluent hemorrhages about the size of a child's hand. The lower arms are altogether swollen and tender (hemorrhages deeply seated?). The right leg is also swollen. X-ray examination of the extremities shows no findings which might indicate scurvy, no subperiosteal hemorrhages, but on the other hand a picture that might correspond with muscular hemorrhages. The bleeding from the prick of the ear soon ceased, but *it seems as if the pressure of the fingers upon the lobe of the ear has been sufficient to provoke hemorrhage within.*

During his stay at The Epidemic Department the patient was highly febrile and the general condition was poor. He was given 3 000 A. U. diphtheria antitoxin. But as the diagnosis diphtheria could not be verified, he was after two days moved to The Department of Pediatrics. Status praesens on April 27th: The boy is listless and exhausted. Foetor ex ore. There is edema on the backs of the hands and the feet. The lower arms and the legs are swollen, firm and tender. An exanthema is spread upon his face as well as on his upper and lower extremities and on his seat. It consists of hemorrhages of different date, from the size of a lentil to that of a child's hand, partly confluent. In the youngest ones the primary lesion seems to consist of a papule, in which secondarily a central hemorrhage appears. In the pharynx there are rubor and swelling with a thick yellowish-white coating on the tonsils. Gingiva: Pronounced rubor and swelling and a greyish-bloody coating. No swelling of the glands. The prepuce as well as the scrotum are red and swollen (subcutaneous hemorrhages). Temperature 39° C. Heart, lungs and abdomen: No abnormal findings. No rigidity of the neck.



Fig. 1. (May 3d).

April 29th. In the course of the first day and night the hemorrhages regressed very much. Beginning last night a considerable swelling has appeared on the face and the whole head, especially in the eyelids and the temporal region, where deep impressions remain from finger pressure. The patient gives an impression of being very sensitive to any touch, he cries loudly when anybody touches him.

May 1st. To-day a new eruption of papular exanthema with and without hemorrhages. The swelling of the face and the head has gradually disappeared. The coating on the tonsils and the gingiva has been exfoliated.

May 5th. The exanthema has gradually changed character. At first most of the lesions were bright red with petechial hemorrhages in the central part. The infiltration of the papules is now less pronounced, while the hemorrhages have increased in size, so that they characterize the efflorescences, which consist of irregular brown spots, the size of a lentil to that of a small coin, rising a little above the level of the skin,

partly confluent. Some hemorrhages have spread in plaques. There are hemorrhages in both auricular conchae, especially in the lobes of the ears. To-day small hemorrhages in the conjunctiva of the eye are observed on both sides. The edemata have almost disappeared. The general condition is good.

May 15th. Until May 10th scattered fresh hemorrhages occurred. After that day no fresh bleedings were seen. There are only faint marks left from the exanthema. The last days he has had a considerable edema of the prepuce and the scrotum, which is now receding.

The temperature reached its maximum 39.5° C. on April 30th, then gradually fell to 37° C. on May 2nd, whereupon there was another, smaller increase in temperature. Normal temperature from May 4th. He was treated with a total of 8.5 gr. sulphathiazole in the time from April 28th to May 2nd. The last week of his stay he was free from symptoms and was dismissed on May 24th.

Table 1 will show the blood findings. Differential count on April 29th: Non-segmented neutrophils: 39 %. Segmented neutrophils: 35 %. Monocytes: 2 %. Lymphocytes: 24 %. Göthlin's test (80 mm. in 3 minutes): No petechiæ. Ophthalmoscopy: No hemorrhages. Lumbar puncture: Normal cerebrospinal fluid. Feces: Benzidine reaction negative. Urine: Heller's reaction negative. No red blood corpuscles by microscopy. Schlesinger's reaction: — 1/10. Takata Ara's reaction negative. Serum colour (Meulengracht): 3. Blood culture: No growth. Culture from the throat: Hemolytic streptococci, *Escherichia coli*. By cutaneous tests no basis was found for nutritional allergy. By intracutaneous tests a strong hemorrhagic reaction with pneumococci was demonstrated. Mantoux 1 mg negative. WR negative.

The clinical picture described corresponds with the one described by SEIDLMAYER, and it may surely be included in the same group. According to SEIDLMAYER the purpura first will appear after a period of weeks of infection. In our patient the infection and the hemorrhages broke out simultaneously, which also happened to one of the patients of OPITZ. The pronounced cephalic and facial edema, the conjunctival hemorrhages, and the hemorrhage in the cavity of the mouth also correspond with the observations of OPITZ. A symptom which was especially marked in our case, was the great tenderness, which might lead the thought towards meningitis. The explanation is presumably to be sought in hemorrhages of the muscles, as both the lower arms and the legs were swollen and firm. A corresponding situation SEIDLMAYER has

found in one of his patients, who had a considerable, very tender swelling of one thigh.

A problem for discussion might be the justification of setting up »Die frühinfantile, postinfektiöse Kokarden-Purpura» as belonging to a disease group of its own. In any case it is closely related to SCHÖNLEIN-HENNOCH's »anaphylactoid» purpura, as regards both the symptomatology and the etiology. It differs from this mainly through the lack of some of the symptoms such as swelling or pain in the joints, abdominal symptoms, proteinuria or hemorrhagic nephritis, as also hemorrhages of the mucous membranes are not present. It seems that this last claim has to be dropped. SEIDLMAYER's description is based on the observation of ten cases. The material is not greater than that the lack of symptoms may depend on chance circumstances.

A further distinction is the age distribution, as SCHÖNLEIN-HENNOCH's purpura particularly occurs after the age of six years, while none of SEIDLMAYER's patients were past three years. Nor is this any decisive difference. It may be imagined that in the early childhood there is a less tendency to development of articular symptoms on the whole, even if the releasing factor is the same, which at a later age might be able to call forth such symptoms. Perhaps »cockade purpura» is the typical manifestation in early childhood of the same disease which at a more advanced age will take on the character of SCHÖNLEIN-HENNOCH's purpura? It seems reasonable to consider SCHÖNLEIN-HENNOCH's anaphylactoid purpura and SEIDLMAYER's cockade purpura as co-ordinate subgroups of a larger main group of allergic purpura diseases. The pathogenetic conditions especially make this interpretation likely.

With regard to etiology and pathogenesis no clarity has been produced. The discussion concerning these questions conforms so greatly regarding the two above mentioned purpura forms, that it may be treated uniformly. The general assumption is an infectious etiology and an »allergic-anaphylactic» pathogenesis. During the course of an infection it is supposed that an allergic condition gradually develops in the organism. SEIDLMAYER arrives at the point of view that the clinical picture may be explained by an antigen-antibody reaction in the capillary endothelium, whereby

Tab.

Date	Hb. %	Red blood corpuscles. Million	White blood corpuscles	Platelets	Clotting time	Bleeding time	Prothro time
27/4	86	4.57	18 400				
28/4				342 000		2 min.	> 5 min.
29/4	83	4.1	32 000				
2/5			49 000				> 5 min.
4/5							> 5 min.
6/5							> 5 min.
8/5							> 5 min.
10/5							> 5 min.
12/5	85	4.8	14 000	480 000	1 min. (?)	1 1/2 min.	1 1/2 min.
15/5							36 min.
17/5							20 min.
22/5							

Tab.

Prothrombin time	Prothrombin time. Parallel test. (Normal individual)	Sedimentation rate	Intracutaneous tests			Cutaneous hemorrhages	Tp.
			Pneumococci	Streptococci	Staphylococci		
						+	39
> 5 min.						+	38.5 38.7
		29				+	39.1 39.5
> 5 min.						+	37.1 37.7
> 5 min.	10 sec.					+	37.6 36.8
> 5 min.						+	Normal
> 5 min.	30 sec.		++++ (hemorrhagic)	—	—	+	Normal
> 5 min.	40 sec.					+	Normal
1 1/2 min.	25 sec.	22				—	Normal
36 sec.	35 sec.		++ (non hemorrh.)			—	Normal
20 sec.	20 sec.					—	Normal
			++ (non hemorrh.)			—	Normal

this is injured and produces the mentioned symptoms: Edemata, urticaria and extravasation of blood. GLANZMANN also has the same conception, emphasizing the post-infectious anaphylactic purpura as the purest form of anaphylactic purpura. HEINILD asserts with support from histological research that purpura (Schönlein-Hennoch) is of allergic nature. He finds in specimens from the efflorescences a necrotizing unspecific hemorrhagic inflammation, especially localized to the vessels. Further endothelial proliferation and fibrinous degeneration, which are stated to be particularly characteristic of an allergic inflammation. His case occurred in connection with an infection, and he points out that the factor which produces allergy, is not the same as the releasing one.

BERGER also interprets this form of purpura as allergic, or partially allergic, possibly with co-operation of phenomena of the SHWARZMANN-SANARELLI type. The reaction is also here released by other microbes than the sensibilizing ones, but otherwise the relations are not clear in this respect. BERGER further states: »Warum die allergische Reaktion in einzelnen Fällen gerade hämorrhagische Diathese macht, ist sehr unklar.« As yet nobody has found any satisfactory explanation of this question. The discussion mostly revolves about a familial or individual way of reaction on the part of the vascular endothelium deviating from the usual. On examinations of families SEIDLMAYER could not demonstrate any hereditary allergic constitution in his ten cases of cockade purpura. On the other hand he found in a series of cases allergic lesions in the ascent of patients with purpura SCHÖNLEIN-HENNOCH (eczema, asthma, migraine, colitis mucosa). He therefore presumes that purpura SCHÖNLEIN-HENNOCH appears in an individual with hereditary taint, while there on the contrary, in the cockade purpura, is an acquired, transient variety of the manner of reaction of the vascular endothelium, released by the infection and running parallelly with the allergization. If it can be confirmed that this difference exists, it is perhaps the best support for the standpoint of SEIDLMAYER of cockade purpura as a special disease.

Infections as cause of allergic lesions have come into the foreground ever more in the last years. In our patient also everything



Fig. 2. Intracutaneous reaction with pneumococci after 2 days.

speaks in favour of the conception that the outbreak of purpura in one way or another is correlated to his acute infection. It might be imagined that the infection with pseudocroup two months earlier was the allergizing factor which left the organism in a highly allergic condition, so that the new infection (angina) immediately released the allergic reaction.

Examinations made in our case serve to illustrate certain aspects of the causative relations of the disease. During the course of the disease several intracutaneous tests with bacterial emulsions were performed (1000 mill. per ml. of respectively pneumococci, yellow staphylococci, hemolytic streptococci, mixed anti-catarthal vaccine). The reaction turned out negatively for all the microbes concerned, except for the pneumococci, which caused a huge reaction with 40 mm. rubor and infiltration and edema in the

surroundings. The reaction reached its climax after twenty-four hours, but persisted for several days, abating gradually. It is interesting that in this papule a central hemorrhage appeared, which spread outwards, so that the reaction presented a perfect picture of the efflorescences characteristic of the disease, only in a somewhat larger scale (Fig. 2). The finding indicates that in this case an allergic reaction to pneumococci is of significance to the development of the hemorrhagic exanthema.

Is it not likely that a so-called »isomorphe Reizreaktion» exists, which occasionally may be seen in skin diseases, as it was only pneumococci which gave the reaction, while the tests with other microbes, which were carried out simultaneously, turned out altogether negatively. Further a Mantoux reaction showed a negative result. Besides, such an unspecific reaction would only be expected during the exudative stage of the actual disease. In our case, however, repeated tests after the disease had become quiescent, still showed a strong allergic reaction to pneumococci.

Smears from nose and pharynx were made in order to get some pneumococci cultivated, and then make intracutaneous tests with the patient's own microbes. We did not succeed, however, in demonstrating pneumococci. This fact does not exclude pneumococci as releasing cause, as they may very well have been contributory to the infection, even if they were not demonstrable at the point of time when the tests were made. Few days after the patient had been discharged, he got pneumonia, and was readmitted into the department. He again received sulphathiazole treatment, and the disease had a regular course. *The prothrombin time was now 20 seconds.* Even if pneumococci neither during the course of the pneumonia were demonstrable, this disease, however, is a basis for the conception that pneumococci may have been instrumental in the infection that produced the purpura. The fact that this last time there was no cutaneous allergic manifestations may be explained thereby, that the organism no longer is in the same allergic condition towards pneumococci, which corresponds to the contention of SEIDLMEYER, that no recurrence of purpura is seen during subsequent grippe infections.

Humoral transmission of the allergic condition from the patient

to a non-allergic individual is otherwise counted as a proof that a reaction is of an allergic nature. Such a transmission has not been reported in purpura. In our case the PRAUSNITZ-KÜSTNER-DE BESCHE's test was performed with a negative result, which was to be expected also, as the antigen-antibody reaction is bound to the cells, not to the tissue fluid or to the serum.

A circumstance of special interest is *the greatly prolonged prothrombin time*. The hypoprothrombinemia thus demonstrated seems to be able to explain the tendency to hemorrhage in this case. Prothrombin examinations, of course, have been carried out in a great deal of cases of hemorrhagic diseases, also in purpura SCHÖNLEIN-HENNOCH, in which it has been found normal by many examiners. NORDENSON states, however, that the prothrombin content of the blood is reduced in this disease. Prolonged prothrombin time in purpura of SEIDLMAYER's type has not been described previously. Neither SEIDLMAYER nor OPITZ mentions this examination in their works. It is of interest in this connection, however, that SEIDLMAYER found prolonged clotting time in two of his patients, in one case considerably prolonged, without mentioning anything about what the cause of this may be. A determination of prothrombin time in these cases might perhaps have shown similar conditions as in our patient.

In our case there seems to be a disagreement between the prothrombin time and the clotting time. No decisive importance may be attributed to this, as determination of the clotting time by mistake was performed only when the prothrombin time approached the normal (May 12th). Besides, the capillary tube method was used, a test which is difficult to evaluate and according to experience gives unreliable results. The prothrombin examinations in the department are performed by a laboratory assistant, who has long experience with the method (the micromethod of Larsen and Plum), and it is our impression that the results are reliable, at least by gross deviations from the normal. Checking-up of the method has shown, however, that it gives somewhat too large values.

We have also undertaken parallel tests with blood from healthy persons, and these constantly showed normal results (20—40 sec-

onds). In this connection it may be of interest to mention the hemorrhages in the auricular conchae, which in our patient were located especially in the lobes of the ears. In the case history of The Epidemic Department has been expressly stated, that it looks as if the pressure on the lobe of the ear during extraction of blood has been sufficient to provoke subcutaneous hemorrhage. This observation suggests that traumata may release hemorrhages, a support for the supposition of a hypoprothrombinemia, as hypoprothrombinemic hemorrhages are released by traumata, while we usually do not see traumatic bleedings in SCHÖNLEIN-HENNOCH's purpura.

In our patient fresh hemorrhages occurred as long as the prothrombin time was prolonged, while they ceased completely as soon as the prothrombin time became normal. It is not likely that this fact depends on an accident. Another support of the supposition is also the result of the intracutaneous test with pneumococci. A test performed while the prothrombin time was prolonged, showed a strong hemorrhagic reaction, while the tests performed after the prothrombin time had become normal, still showed an intense allergic reaction, even though decreasing, but no hemorrhage. The condition on which hemorrhages of this kind may develop, might be supposed to be present, therefore, when an allergic state towards one or another microbe develops in a patient during the course of an infection, simultaneously with the presence of a hypoprothrombinemia (*purpura allergica hypoprothrombinemica*).

It is natural to interpret the hypoprothrombinemia as a consequence of a liver injury, possibly of allergic nature, and released by the same microbes on which depend the cutaneous allergic manifestations. It is not reasonable that the prolonged prothrombin time should be due to K-vitamin deficiency. Nor had an administration of K-vitamins (two injections of 10 mg.) any influence on the prothrombin time of our patient. This might suggest an injury to the prothrombin-forming ability of the liver (cfr. the determination of the prothrombin time before and after K-vitamin injections as a test of liver function), even if other tests of liver function showed nothing pathologic. (Takata-Ara's reaction,

Schlesinger's reaction, Meulengracht's test). It is natural to draw an analogy with the acute infectious exanthemata, which partly must be supposed to be of an allergic nature. It might be imagined that the hemorrhagic cases, also in these diseases, are due to a hepatic injury with hypoprothrombinemia. It is perhaps not so easy to imagine how an isolated damage to one of the partial functions of the liver is to come into existence, without any signs of liver disease otherwise. It does not agree with the experience of WALLGREN about hypoprothrombinemic hemorrhages after the newborn period. In the cases in which he has found that the hypoprothrombinemia depends on a reduced liver function, definite signs of liver disease have always been present (hepatitis, cirrhosis, lues). But any more reasonable explanation of the reduced prothrombin content of the blood is difficult to find in our case. Also from Danish quarters, however, cases have been referred with prolonged prothrombin time during acute infectious diseases, no hemorrhages, however, having occurred in these patients.

The objection may be raised against the infectious allergic genesis, that the serum injection given to the patient in the initial stage of the disease, may have contributed to the forming of the disease. The typical clinical picture, however, was completely developed before the patient got diphtheria serum, and even if the serum injection may have influenced the further course, this cannot make any change in the causal relations mentioned previously.

Summary.

A short description of the conception of disease compiled by SEIDLMAYER: »Die frühinfantile, postinfektiöse Kokarden-Purpura.« The disease occurs in infancy and childhood, up to the age of three years. Most often it is associated with catarrhal infections. It manifests itself through eruption of characteristic purpuric efflorescences, essentially localized to the extensor surfaces of the extremities, and the face, besides urticarial eruptions and a tendency to localized edemata. A case of purpura of this type is referred. Of special interest in this patient were two relations, viz.:

1. An unusually strong, hemorrhagic cutaneous reaction to pneumococci, suggesting an infectious-allergic genesis.

2. A very greatly prolonged prothrombin time (more than five minutes), which could be demonstrated as long as the tendency of hemorrhage existed, and became normal at the same time as the hemorrhages ceased. The possibility of hypoprothrombinemia as a contributory cause of the hemorrhages is discussed.

References.

1. BEGTRUP, H. & HANSEN, F.: Nord. med. 1942, 14, 1851. — 2. BERGER, W. & HANSEN, K.: Allergie. Thieme, Leipzig, 1940. — 3. GLANZMANN, E.: Einführung in die Kinderheilkunde II. Springer, Wien, 1943. — 4. HEINILD, S.: Nord. med. 1943, 20, 2302. — 5. NORDENSON, N. G.: Den kliniska hämatologiens grunddrag. Wahlström & Widstrand, Stockholm, 1940. — 6. OPITZ, H.: »Erkrankungen des Blutes und der blutbildenden Organe«, Handbuch der Kinderheilkunde. Ergänzungswerk I. Ed. v. Pfaundler. Springer, Berlin, 1942. — 7. SEIDLMAYER, H.: Z. Kinderheilk. 1939, 61, 217. — 8. WALLGREN, A.: Nord. med. 1942, 16, 3150.

Familial Congenital Hypertrichosis totalis (Trichostasis).

By

TIELINE A. E. JANSSEN (Zaandam) and
CORNELIA de LANGE (Amsterdam).

Our observation belongs to that kind of hypertrichosis which is generally called hypertrichosis lanuginosa i. e. the persistence, and excessive development, of the lanugo of the fetus. After UNNA's¹ investigation the lanugo is normally shed shortly before birth, which fact explains the relative baldness of the newborn child. Close upon birth the embryonic hairfollicles become shorter all over the body and the hairs are cast. In hairy infants, however, they retain their double length, there being no shortening. WALDEYER² is of opinion that also the number of hairs has increased. Normally the casting of the hairs is followed by the secondary coat of hair. According to WALDEYER and MENSE³, however, the primary hair on the scalp differs from the beginning from the rest of the primary coat, as its follicles normally expand again to double their length. Strictly speaking there is no real hypertrichosis in the hairy infant and the name »trichostasis» of UNNA is a better one than the variation »hypertrichosis lanugonensis s. primaria» given by MENSE.

The hairs in hypertrichosis lanuginosa remain soft and silky and only a few are medullated. In real hypertrichosis the hairiness comes later on and the hairs are markedly strong

¹ P. G. UNNA. Die Histopathologie der Haut. Berlin. 1894.

² WALDEYER, cited after MENSE.

³ K. MENSE. Ziegler's Beiträge. 68. 486. 1921.

and thick. The follicles are first reduced to half their length and in this way a new and gradually hypertrophic coat of hair is formed. COCKAYNE¹ opines that in hypertrichosis lanuginosa in general only the ears are hairy and that the general hirsuties only appears when the child has reached the age of 2 to 7 years. This opinion certainly does not cover all the published cases

It would appear that the lanugo-form may change into a real hypertrichosis. Our compatriot GEYL² has given an interesting and critical review of the question and added his personal observations. One of them has respect to two sisters with marked hair on the scalp and long lanugo on the forehead and cheeks present at birth, but at the age of 2½ years there was a sudden increase in the hair over limbs and body and the hairs grew stronger. The first child had no missing teeth, but there was marked caries dentium, the younger one on the contrary had excellent teeth.

The persisting lanugo or trichostasis produces the dog-faced type; it is hereditary or familial respectively and is accompanied by a poor development of the processus alveolares, a prognathism of the mandible and dental defects of the persistent and occasionally of the deciduous teeth. It may be noted here that congenital alopecia has also been found associated with dental defects both in hairless men and in the hairless Chinese dogs. In real hypertrichosis dental defects are lacking on the contrary and the alveolar borders are hypertrophic. (PARREIDT, cited after MENSE).

ECKER was the first to give a hypothesis of arrested development in trichostasis; the development of the haircoat does not follow the ordinary route, but is arrested in a prior stage. This hypothesis is generally admitted, though GEYL is its opponent. This author calls the anomaly an atavism. One

¹ E. A. COCKAYNE. *Inherited Anomalies of the Skin and its Appendages* Oxford med. Publications. 1933.

² A. GEYL. *Waarnemingen en beschouwingen over ongewonen haargroei*. Dordrecht. Blussé en van Braam. Author's abstract in extenso in *Biologisches Centralblatt*. 8. 332. 1888—1889.

might also ask in how far hormon influences play a part in the process. Neither the above cited authors nor BALLANTYNE¹, who in his *Manual* devotes several pages to the subject of hypertrichosis, gives any information about a microscopical investigation of the skin or a post mortem. It seems that only the hairs themselves have been measured and examined under the microscope. For the rest the literature is rather anecdotal and names and pictures of the same patients constantly recur.

This being the case we venture to give our own observation and though different circumstances preventing us to make the post mortem complete, we yet may be able to fill a lacuna, as BALLANTYNE says: »details of the state of the hairy infant at birth are sadly lacking».

Case History.

LEENDERT, a boy, the fourth child of healthy parents, was born 13. 5. 1944. in a village in the neighbourhood of ZAANDAM. He was born at full term, but weighed only ± 2000 grammes and measured ± 40 cm. The child was first presented at the out patients department. The mother told the following details: Her first child had the same weight at birth as LEENDERT, who resembled him in every way, he was very hairy at birth and his face presented a peculiar appearance. This child died suddenly when four days old. Then followed a sturdy boy of 4250 grammes. He was quite normal at birth, developed in a normal way and is now 12 years old. The third child closely resembled the first, had a low birthweight and died in the same way suddenly at the age of two days without any apparent cause.

LEENDERT was breastfed for six weeks and then was put on artificial feeding. He gained weight slowly, for his weight at the age of $2\frac{1}{2}$ months when presented at the outdoor department (21. 7. 1944), was only 3000 grammes. The feeding is difficult, the child does not empty his bottle. He does not vomit, however, The urine is a dark yellow color, the faeces a light color. The child is still icteric, the jaundice having appeared shortly after birth (the other children were not icteric over an undue period).

¹ J. W. BALLANTYNE. Manual of antenatal Pathology and Hygiene. Book I. 321. 1902. William Green & Sons. Edinburgh.

In the urine a trace of albumin was found, no sugar, urobilin reaction negative, bilirubin slightly positive. Sediment many erythrocytes, some leucocytes. The most striking facts were the child's hairiness and his face resembling that of an anthropoid monkey.

He was admitted to the hospital in ZAANDAM on 3. 8. 1944. with the diagnosis of hypertrichosis lanuginosa and dystrophy. Since the examination on 21. 7. 1944. he had lost some weight. The abdomen was distended by meteorism. No anomalies of the internal organs could be noted, only the spleen could just be felt. The testes had descended and were of normal dimension. The child was still slightly jaundiced. Fontanel sunken, $1\frac{1}{2} \times 1\frac{1}{2}$ cM. Next morning the patient was found dead in his cot without any apparent cause.

The father consented a post mortem, but wished the mother to be left in ignorance of the fact, so that it was not possible to remove the thyroidea. More over conditions of war rendered the autopsy a matter of difficulty and may excuse some omissions which we regret.

POST MORTEM. Length of the body 50 cM. Length of the skull 12.5 cM, breadth 9.5 cM, index cephalicus 76. Both jaws protrude 1 cM beyond the vertical front line giving there by the face the appearance of that of an anthropoid monkey. Also the arcus zygomatici protrude farther than normally. The face wears a senile expression and is deeply lined. The body is covered with a thick coat of fair hair, length at least 1 cM; those on the legs are somewhat shorter and a little less numerous. The face, the borders of the ears, the back, the external sides of the arms are the most hairy parts, while the abdomen and the scrotum seem fairly normal (such regional differences are constantly mentioned in literature). The soles of the feet and the palms of the hands are entirely free from hairs as is normally the case.

The lines in the handpalms and on the soles of the feet are rather deep, but their picture is normal. Both halluces are shorter than the other toes, the left one being in dorsal flexion. The nails overreach the fingertips. The skin is wide and loose, especially so over the buttocks, the fore legs and the fore arms. The buttocks are flat and there is no indent between them. Livores on the back, some discoloration of the umbilicus.

Median section. There is almost no subcutaneous fat, the muscular layer is very thin and is rosy in color; together they measure ± 2 mm. The omentum is very gracile and is lying in a roll against the stomach. Liver dark yellow reaching $2\frac{1}{4}$ cM

below the costal border. Spleen not visible in situ. Intestina of normal appearance with the exception of the coecum that has widened as an ampulla. Appendix length 8 cm. In the mesenterium lymphglands the size of a pea and of glassy appearance. On the right the fifth rib has forked.

The thymus is fairly large. The left lung is violet, the right rosy in hue. The thoracic and abdominal organs were taken out of the body in situ. An excision was made of the skin on the right shoulder for microscopical examination. The organs were taken to the Laboratory of the Emma Hospital for sick Children.

Macroscopical examination.

The *brain* shows its normal configuration, weight 450 Gr. The caudal part of the corpus callosum is lacking; the defect begins at the level of the corpora quadrigemina. The anterior part of the corpus callosum is thinner than usually. Brainstem and cerebellum are separated from the hemispheres by cutting through the pedes pedunculi. The aqueduct of Sylvius looks normal as also sections through the cerebellum. The brain is cut in vertico-frontal sections; nothing abnormal shows. The brain tissue is very soft and very difficult to handle. The hypophysis is lacking and has apparently been lost at the post mortem.

Lungs. The lower lobes of the lungs have more consistency than the upper ones by the hypostasis in the first. Beneath the pleurae of both lungs, small dark spots can be seen, probably hemorrhages. Their number on the left is larger than on the right. No foci of inflammation on palpation. Pressure on the bronchi produces froth.

Heart well contracted, the muscular layer of the left ventricle markedly developed.

Thymus, weight 13.5 Gr, appearance normal.

Liver, weight 112 Gr, color green, dimensions $11 \times 5 \times 3$ cm. Gallbladder present, large bile-ducts permeable (the formalin and the alcohol in which the tissue has been conserved takes on a green hue).

Pancreas, weight 5.6 Gr, nothing abnormal.

Spleen, ordinary appearance and consistency, weight 18 Gr. Dimensions $5\frac{1}{2} \times 4 \times 1$ cm. On section small follicles.

Adrenals, markedly small, together their weight is not yet 2 Gr.

Kidneys, weight of the right one 24.5 Gr, of the left 25.7 Gr, showing a remnant of the fetal lobulation. Capsule has not thickened, medulla and cortex are clearly discernible. The cortex is thin, the pelves have not widened, mucosa not hyperaemic.

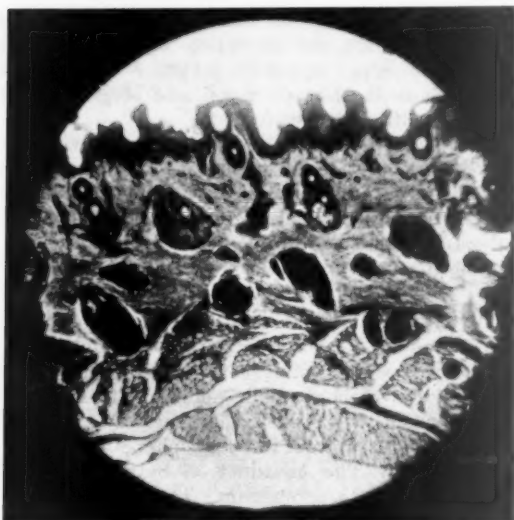


Fig. 1.

Skin over the right shoulder is thickly grown with fair hairs at least 1. cm long and makes the impression of the skin of an animal (dog's skin).

Microscopical investigation.

Brain. The cortex of the examined parts (frontal, temporal and occipital lobes) proved normal. Perhaps by reason of the extreme softness of the tissue the sections of the hypothalamus were far from perfect. It was possible to exclude an inflammatory process or a tumor of this region, also it may be said that the nucleus supra-opticus and the nucleus paraventricularis appeared normal, but the histological sections did not suffice for an examination of the nuclei tuberis, as that part of the tissue was torn up.

Lung. Part of the left upper lobe with pleura. There are hemorrhages in and under the pleura. The alveolar septa have somewhat thickened and some of the bronchi and alveolar ducts contain a small number of erythrocytes. No inflammatory process.

Heartmuscle without anomalies.

Thymus. The difference between cortex and medulla shows clearly. Great number of HASSALS bodies present; the larger ones

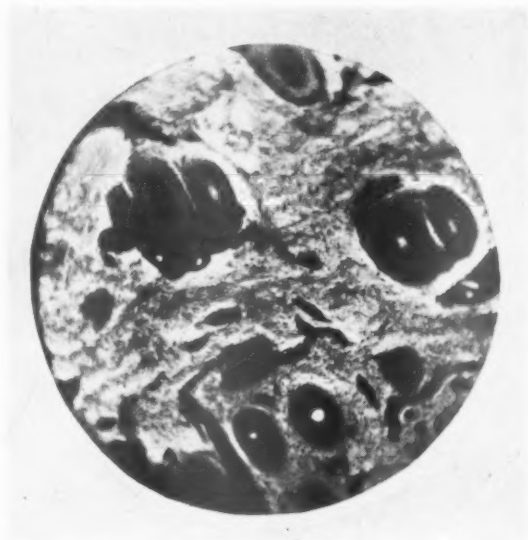


Fig. 2.

often lack the concentric structure (according to COOPER¹ this may be considered as normal for this age).

Liver. The interlobar connective tissue has somewhat increased especially under the capsule. In the portal canals (*espaces porte*) it shows in some spots an infiltration with small cells. The radiar structure of the liver lobules has remained intact, so has the parenchyma itself. In general the blood capillaries are narrow. Some KUPFER cells are swollen. No myeloid foci or isolated myelocytes. One single focus of bloodbuilding is found consisting of elements with a pyknotic nucleus and almost without protoplasm and some somewhat larger cells with a more leptochromic nucleus and broader protoplasm. Bile thrombi are present in large numbers and the liver cells contain a fine yellow-green pigment. The siderosis of the liver is so strongly marked that in performing the reaction of TURNBULL-HUECK the naked eye can observe the sections turning blue. The iron is contained in the liver cells.

¹ EUGENIA R. A. COOPER. The Histology of the more important human endocrine organs at various ages. Oxford. med. Publ. 1925.



Fig. 3.

in the cells of KUPFER and in the adventitial layer of the blood-vessels. It is easy to distinguish the yellow-green bile thrombi and bile pigment in the liver cells from the blue iron pigment.

Pancreas. Taking into consideration that in infants in the first months of life part of the islets of LANGERHANS are rather large, it appears that in our case the number of large islets exceeds the normal. In studying control sections of normal infants the impression is obtained that in the pancreas of the child with the hypertrichosis the total number is also increased, granted, however, that a reliable statement on this point can only be made by comparative numeration in coinciding sections.

Spleen. In general the follicles are rather small. No marked germination centres. Pulpa hyperaemic. Trabeculae normal. Sinus rather narrow, in some spots their endothelium somewhat swollen. The siderosis cannot be compared with that of the liver, it is only moderate in degree and leaves the follicles free. The iron pigment is contained in the reticulo-endothelial cells.

Adrenals. Over the greater part these organs show the physiological degeneration of the primary reticularis, but in some spots

the medullary tissue is more abundant than is generally seen at the age of our patient.

Kidneys without anomalies. The neogene area still clearly visible, no siderosis.

Skin. Sections of the skin of the hairy infant were compared with those of two normal children of the same age, also taken from the shoulder and cut with the microtome over equal breadth (10 μ).

As might be expected there was a difference in the number of hairfollicles between the two pieces of normal skin, but the difference between them both and the pathological skin was of quite another order. Here they were much more numerous especially in the deeper parts of the corium and as normally only few hairfollicles are lying in the subcutaneous fat tissue, here on the contrary many of them were found there. (Fig. 1, 2, 3.) Part of the deeply situated follicles were very intensely stained by the hematoxylin. On first looking one saw only deeply stained little spheres, but on examining them more closely the nuclei of the follicle epithelium were discovered. The number of sudoriparous glands seemed somewhat less than normal.

Discussion.

How can the mors subita of this child and of the two former ones be explained? The opinion of TARDIEU that subpleural hemorrhages are proof of death by asphyxia cannot be held. In a majority of cases the cause of an unexpected death in infants lies in a capillary bronchitis or in an incipient pneumonia surcharging the body with toxical products. In the case of the child L. v. R. there are neither clinical nor anatomo-pathological reasons to assume this cause. Also it would be a strange coincidence should all children have died in this same way. Therefore no answer can be given as to the cause of the child's sudden death.

A striking fact was the small size of the adrenals, as one would be inclined to expect here enlarged organs with cortical hypertrophy. It is to be regretted that no microscopical examination has been made of the testes; their dimensions were normal.

The excessive siderosis of the liver recalls an icterus gravis familiaris on the way to recovery, but the details respecting the other children practically exclude this diagnosis. Probably

there has been an icterus neonatorum of long standing with destruction of blood on a large scale. In recent years the vegetative centres in the hypothalamus and especially in the regio tubero-infundibularis have acquired a place in the lime-light with regard to the etiology of diseases of internal secretion. If in future a post mortem in a case of trichostasis proves possible, a thorough examination of these centres will be necessary together with that of the hypophysis.

To conclude: our observation supports ECKER's hypothesis which explains the congenital hairiness as an arrested development of the haircoat and WALDEYER's opinion that the number of hairs has also increased and it is the first which gives a post mortem and a histological examination of the skin.

FROM THE PEDIATRIC CLINIC (HEAD: PROFESSOR STURE SIWE) AND
THE RADIOLOGICAL DEPARTMENT (HEAD: DOCENT HANS HELLMER),
UNIVERSITY OF LUND.

Clinical Appearance and Diagnosis of the Colon Polypus.¹

By

JOHANNES LEWIS-JONSSON.

The clinical picture of the colon polypus has long been familiar. A. STOLTZ published a comprehensive study as early as 1831, and C. GERHARDT, professor in Jena, gives a very good description in his textbook from 1871, laying particular stress on the easily diagnosed rectal polypus. In 1895 EDUARD HENOCHE mentions that polypous tumours in the colon mucosa are not rare. They are mostly to be found in the rectum some centimetres above the sphincter, where they may grow to the size of a plum and finally join up with their starting point by means of a long pedicle of varying length. The figures published in 1924 by the pathologist STAEMMLER show that the high frequency of this localization is not due solely to the rectum's being more accessible to diagnosis: Among 17 000 post-mortem cases he found 116 intestinal polypi, of which 102 were localized at the colon and 43 of these at the rectum. The colon polypus is more common in boys than in girls. It may be of multiple localization as in case No. 3 below. As pointed out by the Danish author HANS TÖNNESEN, it is necessary to differentiate clearly between multiple solitary polypi and polyposis coli. In the first case the disease picture is only changed by the growth of the already present polypi, while in the latter the new formations show different phases of development, and new polypi are formed continuously.

The clinical picture in cases of colon polypus is dominated by blood in or on the faeces. The higher the site of the polypus

¹ Communicated in a shorter and slightly different version at the meeting of the Sydsvenska Pediatriska Förening, in Hålsingborg Dec. 17, 1944.

the more will the blood be mixed with the rest of the intestinal contents, while the presence of a polypus situated lower down is shown by a streak of blood on the faeces or by causing an outflow of fresh blood from the anus (see case 2). The intermittent nature of the bleeding should be remembered — it lasts for some days, and then disappears again. When a polypus is suspected, the physician himself should examine the faeces, as a laboratory examination for blood may easily be performed on a part of the faeces which does not contain any blood.

Mucus on the faeces may be a symptom of colon polypus: a great deal of it points more to polyposis with villous polypi. The rectal polypus may sometimes be placed in such a way that it emerges from the anal ring at defaecation, and can be observed directly. A large polypus in the colon may so obstruct the passage of the intestinal contents that there may be risk of ileus. Pains in the left lower part of the abdomen are not infrequently described. A polypus in the upper part of the colon may cause invagination. Colon polypus, as all polypi, involves the risk of malign degeneration, especially in the basis of the pedicle. The most common clinical picture, however, is the one where blood on the faeces or bleeding per anum is the only symptom.

The bleeding ought to draw the clinician's attention to the presence of an affection in the intestines, and, if colonic polypus is suspected at all, the diagnosis in a well-arranged investigation is quite easy. As a rule the patient is diagnosed late, partly owing to the variable nature of the symptoms and partly because there is often a certain tendency to make light of the symptom of blood on the faeces, which is very wrong in the case of children. HENOCHE mentions that he has certainly seen hemorrhoidal nodes in children, even in a child of 3 years, but he has never met with bleeding. He is of the opinion that the polypi are the most common cause of bleeding from the colon in childhood.

The available diagnostic methods of investigation are rectal exploration, rectoscopy and radiological examination; and these methods ought to be performed in this order.

Rectal exploration is generally performed with the patient in the dorsal position. ROVSING advocates palpation with the patient

in a squatting position; the patient is then told to press down the tumour by straining, which makes it possible to reach even a rather highly placed polypus. Even if the patient states that the polypus has emerged outside the anus it may be difficult to reach it in rectal palpation.

Rectoscopy is very valuable for determining the diagnosis and should never be omitted when there is the least suspicion of colon polypus. It is true that rectoscopy of children is in a special class: It may be hard to make the child co-operate at the investigation, a rectoscope for children affords a smaller range of vision on account of its narrower diameter, in which it is not always easy to detect a polypus. Purging and irrigation may have to be performed several times before the intestinal mucosa is clean enough to permit a satisfactory examination.

Even if rectal exploration or rectoscopy give positive results, the colon ought to be examined with X-ray, as one or more polypi may be present higher up in the intestine. In cases of polypi situated above the reach of the rectoscope, a radiological examination is the only means of diagnosis. To give certain results it requires special methods. It is therefore the clinician's duty to draw the roentgenologist's attention to the possible presence of a polypus. This point of view was stressed by HANS HELLMER in 1933; regarding the technique of the examination see his work (*Röntgen-praxis* 1933: 5: 21). The radiological examination must be able to show a constantly recurring defect in the contrast shadow, which may change its position according to the pressure of the contrast fluid if the radiogram is to be pathognomonic of a colon polypus. One of the conditions of a good roentgenogram is an effective opening of the bowels, which is not always so easy to obtain when the colon is the site of one or more polypi.

* During the last 2 years 3 cases of colon polypus have been treated at the Pediatric Clinic in Lund, each in its separate way illustrating what has been said above. The case histories are therefore summarized below.

Case I. Journ. Ped. Clin. No. 1124/43, girl, 2½ year old. Time of treatment 7.12—12.12 1943. Diagnosis: Polypus coli sigmoidei.

Anamnesis: Period of diarrhoea 3 months earlier. When the faeces



Case I.

began to be solid, the mother observed a streak of blood on them. She went to a physician, who advised expectant treatment, and, when there was blood on the faeces every day, to another physician, after which the patient was admitted to the Ped. Clin.

State: General condition good. Hemoglobin test (Sahli) 100 %, erythrocyte count 5.1 mill., Micro-sedimentation rate 6/14 mm. Abdomen: No palpable pathological resistance. Per rectum: Nothing pathological palpable. Roentgen examination of colon: About 12 cm above anus a rounded polypus measuring about 1 cm in diameter. It has a relatively short pedicle, about 1 cm long. Otherwise nothing abnormal (Hellmer).

Case II. Journ. Ped. Clin. No. 1084/44, girl, 6 $\frac{1}{2}$ year. Time of treatment: 4.12—13.12 1944. Diagnosis: Polypus recti cum hemorrhagiæ.

Anamnesis: Treated at the Ped. Clin. 26.8—1.9 1944 on the diagnosis: Gastroenterocolitis acuta, and 13.9—22.9 1944 on the diagnosis: Observation (Haemorrhagia ex intestine??). On return home after the first stay in hospital the patient had complained of pain in the left part of the abdomen, and at defaecation 11.9 and 12.9 blood was observed on the faeces. During the patient's stay in hospital palpation of the rectum showed nothing abnormal, radiological examination of the colon also gave a normal picture, and Weber's test was negative on 3 occasions. Rectoscopy was not performed. — The patient came back to the hospital 4.12, this time as an acute case, as the mother had found a large blood stain with clots in the girl's bed one morning.

State: Somewhat pale. Hemoglobin test 75 %. Erythrocyte count 3.0 mill. Micro-sedimentation rate 3/9 mm. Bleeds per rectum, bled about 160 ml during the first 24 hours, after that no bleeding. Abdomen: No pathological resistance palpable. Per rectum: Nothing pathological palpable, with the exception of blood on the glove. Rectoscopy: Position à la vache. 8 cm upwards a polypus about $\frac{1}{2} \times \frac{1}{2}$ cm appears in the field of vision. It has a short pedicle. Its mucosa does not differ from the rectal mucosa except for a small erosion at the back of the apex. It does not bleed now. Examination upwards, to 12 cm from the anus, shows nothing abnormal. Radiological examination of colon: At a spot agreeing with the rectoscopy finding, i.e. about 8 cm from the anus, there is an irregular outline which cannot be more exactly analyzed by radiological examination. Otherwise normal colon. In the present case the diagnosis must be based solely on rectoscopy (Hellmer).

Case III. Journ. Ped. Clin. No. 1078/44, boy, 3¹¹/₁₂ year. Time of treatment: 1.12—21.12 1944. Diagnosis: Polypus recti et coli sigmoidei.

Anamnesis: In Febr. 1944 bright blood was one day observed on the faeces. The same happened again in March. During Spring the patient sometimes came in from playing, complained of »tummy-ache», and went to bed. In June there was 1—2 solid faeces daily with blood. After having been treated on two different occasions at another hospital on the diagnosis: Colitis et Enterocolitis acuta, the patient came to this clinic, as blood had again been observed on the faeces. He was admitted for observation.

State: General condition good. Hemoglobin test 95 %. Erythrocyte count 4.3 mill. Micro-sedimentation rate 26/35 mm. Abdomen: No pathological resistance palpable. Per rectum: No pathological resistance palpable. Consistency of faeces varies, sometimes loose and mixed with mucus. Weber positive at 2, negative at 12 examinations. Rectoscopy: After several attempts good range of vision is obtained on 5 different occasions by means of purging and irrigation. Position à la vache. 7 cm upwards a new growth is observed in the field, slightly bigger than a hazel-nut. Its surface is partly covered with fibrin. No bleeding. The



Case III.

mucosa below and a further 3 cm above, normal. Radiological examination of colon: The contrast fluid injection in the colon shows within the rectal part of colon sigmoideum about 14 cm above anus a filling defect which measures 13 mm in diameter and oral to it a larger filling defect with a diameter of 3 cm. Both filling defects have irregular outlines and rounded shape. The larger one can be shifted slightly. The defects represent polypi (Olle Olsson).

Summary.

The solitary pedicled colon polypus offers a complex of symptoms which will nowadays lead to a certain diagnosis, if only the possibility of this disease is borne in mind, and the investigation arranged accordingly. Rectal palpation, rectoscopy and radiological examination according to the methods given for colon polypus are the three diagnostic methods which must all be used. Three cases of colon polypus in children are reported: one with threatening bleeding and one with three polypi, one of which was diagnosed with the rectoscope and the other two by means of X-ray.

References.

DAHL, ROBERT: Sv. Läkartidn. 1932: 43: 1137. — GERHARDT, CARL: Lehrbuch der Kinderkrankheiten, Tübingen 1871. — HELLMER, HANS: Röntgen-praxis, 1933: 5: 21. — HENOCHE, EDUARD: Vorlesungen über Kinderkrankheiten, Berlin, 1895. — ROVSING: Münch. Med. Wschr. 1908: 38: 1456. — RUDBERG, SVEN: Nord. Med. 1941: 9: 524. — STOLTZ, A: Journ. f. Kinderkrankh. XXXIV: p. 393, quoted from Gerhardt. — STAEMMLER, M.: Deutsche Zschr. f. Chir. 1924: 46 A. — TÖNNESEN, HANS: Polyposis gastrointestinalis, Köpenhamn 1931.

Gastro-Duodenal Ulcer in Childhood.

By

ERIK WAMBERG.

Gastric as well as duodenal ulcer is regarded as a rare occurrence in childhood, and Scandinavian literature contains but few case reports on the subject. In the course of one year our Department has received two children with typical duodenal ulcers demonstrable by X-ray. The main symptom in one case was vomiting, in the other hæmorrhage.

Case History I.

Case Rec. 387/1944 H. M. Admitted Febr. 9, discharged Mar. 26, 1944. An otherwise healthy girl, aged 9. No family history of duodenal ulcer. For the last 5 years the child had been suffering from periodical vomiting. The attacks did not seem to display a tendency to increase. They usually lasted for about 3 days with intervals up to 6 months without being seasonal. The vomitings had been violent, occurring repeatedly in the course of the day without relation to meals. Melæna and hæmatemesis had not been observed. Stools and urine normal.

Obj. exam.: Appearance natural. Nutrition medium. Apart from hypertrophic tonsils and adenoid vegetation in the pharynx, the objective examination failed to reveal any abnormalities, especially of the abdomen which was normal and without tenderness. Hæmoglobin: 94 per cent, blood sedimentation: 4 mm/1 h., Wassermann test negative, Mantoux negative. Urine normal, faeces ÷ blood. Ewald I 3/4 hours: quantity 200 + 24 ml. Congo/phenolphthalein 26/40, fairly chymified, no mucus. Ewald II 3/4 hours: quantity 100 + 75 ml. Congo/phenolphthalein 21/40, well chymified, no mucus. Kemp's test meal showed no retention after 12 hours. Roentgenogram of the stomach and duodenum showed signs of pyloric stenosis, the stomach being atonic and ectatic with ample contents of fluid and emptying very slowly. At the top of the duodenal

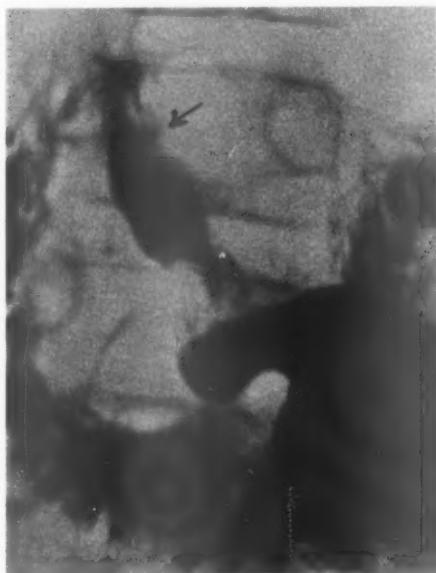


Fig. 1. Case I: At the top of the duodenal bulb there is an ulcer on the lesser curvature (indicated by the arrow).

bulb there was a remnant of contrast material visible on all the plates (Fig. 1). Roentgen diagnosis: Duodenal ulcer — pyloric stenosis.

No dyspeptic symptoms were observed during the stay in hospital. The patient received and tolerated a nearly full diet and gained in weight. Feeling well on discharge.

Summary of the Case. A 9-year-old girl had been suffering from periodical vomiting for 5 years without other symptoms. X-ray revealed the cause of the symptoms to be a duodenal ulcer attended with pyloric stenosis.

Case History II.

Case Rec. 1317/1944, B. C. Admitted Sept. 27, discharged Oct. 22, 1944. Otherwise healthy girl, aged 11. No family history of duodenal ulcer. The disease had begun suddenly 2 years ago with »pain in the



Fig. II. Case II: Deformity of the duodenal bulb. An ulcer (indicated by the arrow) on the greater curvature.

stomach», vomiting, and melena. She was admitted to a department of medicine at a provincial hospital, where she was submitted to a dietary treatment. Symptomless after the lapse of 6 weeks. On admission she had been extremely anæmic. Ewald's test meal of a large quantity with slightly enhanced acidity; there was some blood in the fæces and X-ray revealed a slow emptying of the stomach with 4 hour's retention. Otherwise nothing abnormal. During the 6 months following discharge the patient suffered from frequent attacks of abdominal pain, gradually decreasing in order to cease completely in the course of the summer of 1944. In the middle of September 1944 the symptoms re-occurred, now attended with fatigue. A week later melæna was observed for which reason the patient was admitted to our Department.

The patient and her mother stated that the pain had appeared periodically, lasting for 1—2 weeks at a time with painless intervals of several months, as a rule quite absent in the summer. The pain was localized to the centre of the epigastric region, never radiating. It occurred at all hours of the day, preferably when the patient was hungry

or cold, but never in the night. The pain was aggravated by muscular stress and psychic actions, but relieved by eating and pressure against the epigastrium. No vomiting (for the last 2 years) or hæmatemesis.

Obj. exam.: A pale, not debilitated child in a satisfactory state of nutrition. Tissue turgor good. Steth. cord.: slight systolic murmur. Otherwise the general objective examination revealed no abnormalities, especially no tenderness of the abdomen. Hæmoglobin 44—38—92 per cent, blood sedimentation: 2 mm/1 h., Wassermann test negative, Mantoux negative. Leucocyte and differential count as well as thrombocyte count revealed normal values. Bleeding and clotting time, prothrombin time and ascorbic acid tolerance test normal. Urine: ÷ albumin, blood and pus, a few times + sugar, ÷ diacetic acid, ÷ acetone. Glucose tolerance test with 27.4 g. glucose gave a normal blood sugar curve. Fæces: Melæna for the first few days, later 3 times ÷ blood. Ewald 3/4 hours: quantity 120 + 17 ml. Congo/phenolphthalein 41/56, well chymified, no mucus. Kemp's test meal showed no retention after 12 hours. X-ray of the stomach and duodenum revealed a normal stomach, but a deformity of the duodenal bulb with a niche on the greater curvature, 1 cm. distally to the lateral recess (Fig. II). Roentgen diagnosis: Duodenal ulcer.

Apart from some nausea and a few vomitings, not containing blood, in the beginning of her stay in hospital, the patient did not exhibit any dyspeptic symptoms at all. She was put on a purée diet, gradually rising to a nearly full diet. Besides, she received one blood transfusion (500 ml.) and Ferrosi tartras. She gained in weight and was feeling well on discharge.

Summary of the Case. An 11-year-old girl had been suffering from periodical pain in the epigastrium for the last 2 years, especially when exposed to hunger or cold. Severe melæna twice. X-ray revealed a typical duodenal ulcer.

Ulcerations in the stomach and duodenum are not equally common in all age groups. The morbidity is considered to be highest during the first year of life, decreasing rapidly during the subsequent years in order to rise around puberty. The two-dented curve formed by the morbidity presumably is due to the fact that the ulcers occurring in infancy as a rule have a pathogenesis different from those appearing in later childhood.

According to the literature *children below 5 years of age only*

exhibit gastric or duodenal ulcer sui generis in extremely rare cases. KUNDRAT, FINKELSTEIN and THEILE thus contend that the disease does not occur before the 5th year of life. By a perusal of the literature I have only been able to find 2 case reports (REIMER and MICHAELSSON) of apparently primary, «chronic» ulcers in this age group, whereas ulcerations arising from other causes are not at all rare findings in the stomach and duodenum. BERGLUND's autopsy material contained ulcers in 1.54 per cent of children below 1 year of age and SCHMIDT observed 1.8 per cent in the same age group. Ulceration is an especially frequent phenomenon among children below 6 months of age, mainly during the first few days of life. These ulcerations, which occur with equal frequency in both sexes, as a rule are situated in the duodenum, solitary in more than 70 per cent of the cases and localized on the posterior wall orally to the papilla of Vater.

Presumably the ulcerations in all such cases should be regarded as *secondary* (THEILE, FINKELSTEIN) following infections (sepsis, pneumonia, measles, scarlet fever, diphtheria, erysipelas, tuberculosis, syphilis etc.), intoxications (nephritis with uræmia), traumata, circulatory disturbances, burns, and states of cachexia (pedatropy). Reports have also been published of ulcerations arising in connexion with pneumococcic, meningococcic, and tuberculous meningitis, but it is not known with certainty whether these ulcerations are due to the infection as such or possibly are neurogenous.

According to earlier investigations (HOLT, ADLER) a large number of these secondary ulcerations are attended with melæna or hæmatemesis, vomiting, diarrhoea or constipation. In some cases in this age group, however, the first sign of a gastroduodenal ulcer may be peritoneal symptoms with collapse in consequence of perforation. About one-third of the cases are symptomless, however, (HOLT) and a definite diagnosis can hardly be passed in vivo.

The prognosis is considered to be poor, depending of course primarily on the course of the original disease. In case of perforation the prognosis is extremely bad for these already debilitated children, but according to WIEDERHOFER (1880) it is

extremely serious too in cases attended with melæna. It cannot be decided with certainty, however, whether the diagnosis of gastro-duodenal ulcer in some of these early reports had been passed on the basis of melæna alone, so the materials may contain cases of hæmorrhage arising from other causes than ulcers. Whether this is the case or not, the introduction of vitamin K treatment has made a revision of the prognosis for melæna necessary.

As emphasized in the foregoing the comparative frequency of gastric and duodenal ulcers in this age group is a result of the difference between the pathogenesis of the ulcerations appearing in this age group and that of ulcerations occurring in later childhood. In this connexion it is worth mentioning that the sex distribution among young children is equal, whereas the boys outnumber the girls in the later age groups.

Children above 5 years of age also may exhibit secondary ulcerations following severe infections and intoxications, but not as often as infants. In this age group, however, the vast majority of the cases represent actual gastro-duodenal ulcers as encountered in adults.

The reports on the frequency of gastro-duodenal ulcers in older children are sparse and mostly fetched from the autopsy table. SCHMIDT and BERGLUND found these ulcers in 0.6 per cent and 1.2 per cent respectively among children aged 2—13 years, whereas HIRSCH only found a percentage of 0.3—1. Finally, BRINKMANN observed ulcers in 11 patients below 20 years of age (0.2 per cent) from among a material of 5 493 autopsies of all age groups. From an X-ray material of 911 patients in all age groups with roentgenologically demonstrable ulcers MICHAELSSON found 14 cases among children below the age of 15 (i. e. 1.5 per cent). DEUTICKE has tabulated the operative statistics of gastric and duodenal ulcers reported by the following authors:

BIRGFELD: in the 1st decennium 0.3 per cent; in the 2nd decennium 2 per cent of all cases.

WANKE: in the 1st decennium 0.6 per cent; in the 2nd decennium 0.5 per cent of all cases.

WYDLER: in the 1st decennium 0.4 per cent; in the 2nd decennium 1.2 per cent of all cases.

PROCTOR found only 3 children under 14 years of age among 8 263 patients. The figure no doubt is unusually low, but other clinical studies of the frequency do not seem to have been made.

The last 25 years have, however, brought case reports of gastro-duodenal ulcers in older children and a few compilations (THEILE 1919, PROCTOR 1925, WEBER 1925, DEUTICKE 1936). According to the last-mentioned author the number of cases known up to 1936 was 74. The reports published during recent years, however, have augmented the number of gastric and duodenal ulcers in children more than 5 years of age up to an estimated figure of about 100. 16 of these cases have been published in Scandinavian literature during the last 20 years: KÅRSTAD 1924 (2), NORRLIN 1924 (1), HOLM 1929 (2), MICHAELSSON 1926 (3), PAUS 1927 (2), K. M. ANDERSEN 1929 (1), SUNDAL 1939 (1), ALSTED 1941 (1), OLUF ANDERSEN 1941 (1), THYSSSEN 1941 (1).

In children as well as in adults the cause of the disease cannot be definitely ascertained, but no doubt the part played by heredity should not be overlooked. KALK reports to have found hereditary predisposition in 75—80 per cent of all patients below the age of 20 (in the case of adults STOLL, WESTPHAL, and HUBER found a family history in 13, 25, and 15—33 per cent respectively).

According to the literature the disease has been observed more commonly in boys than in girls, and, like adults, children mainly seem to exhibit the lesion in the duodenum.

The symptoms are extremely varied, but as a rule the disease manifests itself in one of the following manners:

(a) With the classic »Syndrome pylorique» consisting of periodical, tardy pain in the epigastrium, relieved by the intake of food, possibly later followed by violent, acid vomiting, and hæmorrhage, exactly like the symptoms observed in adults. Quite a large number of the cases are attended with hypersecretion and

retention. This syndrome is, however, rare, presumably because children give inaccurate information about their symptoms.

Cases referable to this group have been reported by DIENST-FERTIG, WEBER, MICHAELSSON, PAUS, HIRSCH, DEUTICKE, SUNDAL, and ALSTED.

(b) After a symptomless course the disease suddenly manifests itself by the appearance of the complications: melæna, hæmatemesis, or perforation, in the last-mentioned case with the usual symptoms of peritoneal irritation. In a number of cases with perforation the pain, strangely enough, has primarily been localized to the right iliac fossa.

This syndrome seems to be more common among children than among the adult patients, a phenomenon which, as stated below, no doubt is due to the fact that the disease rarely is recognized except when appearing with the typical symptoms.

This group includes several of the cases reported by THEILE, furthermore those described by NORDENTOFT, HOLM, and part of those reported by KÅRSTAD.

(c) With uncharacteristic dyspeptic symptoms: nausea, vomiting immediately after meals, a feeling of pressure in the »stomach» or pain referred to the lower epigastrium, right iliac fossa or other parts of the abdomen, and often, as is the custom of children, to the umbilical region. In these cases the pain appears at all hours of the day without definite relation to meals.

Cases referable under this heading maybe constitute the largest group and conceivably often escape recognition until hæmorrhage or perforation reveal the nature of the disease. There is good reason to believe that the application of X-ray examinations often will surprisingly reveal a gastric or duodenal ulcer as the causative factor of uncharacteristic dyspepsia in childhood (uncharacteristic dyspeptic symptoms had been present in 7 of MICHAELSSON's 14 cases diagnosed by X-ray).

The complications appear in the form of cicatricial changes with stenosis, penetration and perforation with an earlier onset and apparently greater frequency than in adults. According to KALK even the youngest age groups may exhibit severe anatomical

changes with pronounced functional disorders which adults as a rule only acquire after the lapse of years. In 5 out of 11 patients STOCKER (cited by DEUTICKE) demonstrated severe changes at operation. Among the complications perforation deserves most notice. The fact that it is more common among children than among adults is evident from the statistics comprising the years 1925—30 which statistics also show that perforation as well as the other complications have considerably decreased in frequency during recent years on account of the improved diagnostic means and increased attention. PROCTOR's material from 1925 thus contained perforation in 33 per cent and pyloric stenosis in exactly the same percentage, whereas DEUTICKE observed perforation in 16 per cent and pyloric stenosis in 10 per cent of the cases published during the period 1926—1936.

The diagnosis does not afford difficulties, if the child exhibits the symptoms characteristic of gastro-duodenal ulcer in adults, but abdominal pain and vomiting are frequent phenomena during childhood (school age). Acute appendicitis, enterocolitis, constipation, calculi, as well as infections in the urinary tract *may* be the etiological factors of abdominal pain, but as established recently by BENT ANDERSEN a great part of the »stomach ache» experienced by children is explicable by a bad environmental influence and may be brought to a stop by changed surroundings. No doubt, however, the symptoms of numerous children are neglected for years, whereas other cases are taken as »chronic appendicitis», »umbilical colic» or the effects of a presumed tabes mesaraica, and finally a large number of cases of abdominal pain in childhood have been put down to the presence of helminthiasis.

The diagnosis is, however, complicated by the inaccurate data supplied by children and the fact that they are apt to refer all sorts of pain to the abdomen. Therefore, it is difficult to set up general rules for the cases in which gastroduodenitis should be kept in mind as a possible cause of the symptoms. In some cases, however, a patiently recorded anamnesis will afford the clue to a diagnosis of gastroduodenal ulcer, whereas other cases are revealed only by X-ray or by the appearance of complications.

The prognosis is stated to be poor with respect to duration

and cure, careful roentgenological examinations and operations having demonstrated that the ulcerations display a minimal tendency to heal (KALK). Moreover, there is a major tendency to recurrence (HIRSCH). With respect to the life of the patient the prognosis presumably is good, in spite of the chance of perforation or repeated hæmorrhage.

As to *treatment* the same principles apply to the disease in childhood as in adult life. Surgical treatment applying gastro-enterostomy which formerly was so widely used also has been tried on children who, however, also have exhibited typical post-operative peptic jejunal ulcers (TIEGEL, NYSTRÖM, MICHAELSSON and others). For this reason DEUTICKE recommends extensive resection as a standard method in cases revealing no improvement upon conservative treatment and in which repeated X-ray control has failed to display a tendency to heal. It must be kept in mind, however, that such an operation will entail a lifelong achylia, maybe with the attendant conditions (reduced gastric digestion with gastrogenic diarrhoea and anæmia due to deficiency) and that the primary operative mortality is stated to be higher than among adults (HIRSCH). Consequently, it must be emphasized that recurrences call for a *conservative* treatment carried out with even greater patience than in adults. Surgical intervention must be considered as the last way out and only called for in cases of severe stenosis and perforation.

Conclusion.

(1) It is impossible to state the frequency of gastroduodenitis with or without ulcer in childhood, but it is not at all improbable that the cases reported in the literature leave an impression of a too low figure.

(2) In adults the diagnosis is primarily based on the anamnestic data given by the patient regarding the pain experienced (sometimes later confirmed by X-ray), but a definite diagnosis is seldom to be based on the data supplied by children regarding pain. In childhood, therefore, the diagnosis of ulcer as a rule is not established until the complications occur, viz.

hæmorrhage, stenosis, perforation. For this reason the complications are (perhaps only apparently) more frequent among children than among adults.

If X-ray were used more extensively than it presumably is for the examination of children exhibiting the above-mentioned dyspeptic symptoms, it would no doubt contribute to reducing the dominance of the complications by making the diagnosis easier.

Summary.

The writer reports the case histories of 2 girls, aged 9 and 11 respectively. The younger girl had been suffering from periodic vomiting for 5 years, whereas the other patient had suffered from vomiting for 2 years as well as periodic, partly tardy pain in the epigastric region and exhibited melæna twice. In both patients Ewald's test meal was of a large quantity and X-ray examination revealed a typical duodenal ulcer.

Ulcerations of the stomach and duodenum are most frequently encountered in the first year of life and around puberty. In infancy the ulcers nearly always have appeared in conjunction with infections, intoxications, traumata, circulatory disorders, burns, or cachexia, but the ulcers occurring in children above 5 years of age in the vast majority of cases are based on actual gastroduodenitis.

The disease may manifest itself by (a) a gastroduodenitic syndrome just as in adults, (b) the sudden occurrence of complications (hæmorrhage or perforation) and finally, presumably most often by (c) vague and uncharacteristic symptoms.

Mention is made of complications and differential diagnosis. The treatment should be conservative, considering that the operation most in use for the moment (resection), which presumably is the only rational surgical treatment, entails a high primary mortality apart from being apt to cause lasting disorders. Operation is called for only in cases of severe stenosis and perforation.

In the conclusion the writer emphasizes that gastro-duodenal ulcers in childhood presumably occur more frequently than is

generally supposed and that a more extensive use of X-ray in the examination of children with uncharacteristic dyspeptic symptoms no doubt would lead to a recognition of ulcer more frequently than the procedures used at the present moment.

References.

- ADLER, H.: *Am. J. M. Sc.*, 1907: 133: 135. — ALSTED, G.: *Ugeskr. f. Læger*, 1941: 103: 179. — ANDERSEN, BENT & DALGAARD, F.: *M. f. p. Lg.*, 1943: 21: 373. — ANDERSEN, K. M.: *Ugeskr. f. Læger*, 1929: 91: 978. — ANDERSEN, OLUF: *Ugeskr. f. Læger (Disc.)*, 1941: 103: 180. — ARMITAGE, H. M.: *Ann. Surg.*: 1927: 85: 632. — BERGLUND, N.: *Acta paediat.*, 1928: 8: 323. — BRATUSCH-MARRAIN, A.: *Wien. klin. Wehschr.*, 1933: 46: 417. — BROCHINGTON, C. & LIGHTWOOD, R.: *Lancet*, 1932: 2: 1209. — DIENSTFERTIG, A.: *Deutsche med. Wehschr.*, 1923: 49: 1017. — DEUTICKE, P.: *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1936: 44: 290. — FINKELSTEIN, H.: quoted by HIRSCH. — GUTRIE, K. J.: *Nord. med.*, 1943: 17: 480. — HARTUNG, C. & WARKANY, J.: *J. A. M. A.*, 1938: 110: 1101. — HIRSCH, W.: *Monatsschr. f. Kinderh.*, 1935: 63: 429. — HOLM, E.: *Ugeskr. f. Læger*, 1929: 91: 649. — HOLT, L. E.: *Am. J. Dis. Child.*, 1913: 6: 381. — KALK, H.: *Ztschr. f. klin. Med.*, 1928: 108: 224. — KUNDRAT: quoted by THEILE. — KÅRSTAD, J.: *Acta chir. Scandinav.*, 1924: 56: 82. — MICHAELSSON, E.: *Acta chir. Scandinav.*, 1926: 59: 139. — NORDENTOFT, J.: *Acta chir. Scandinav.*, 1927: 62: 426. — NORRLIN, L.: *Acta chir. Scandinav.*, 1924: 56: 309. — PATERSON, D.: *Lancet*, 1914: 1: 63. — PAUS, N.: *Acta chir. Scandinav.*, 1927: 61: 40. — PROCTOR: quoted by DEUTICKE. — REIMER: quoted by MICHAELSSON. — SCHMIDT: quoted by BERGLUND. — SUNDAL, A.: *Nord. med.*, 1939: 4: 3376. — Thyssen, E.: *Ugeskr. f. Læger*, 1941: 103: 615. — THEILE, P.: *Ergebn. d. inn. Med. u. Kinderh.*, 1919: 16: 309. — WEBER, M.: *Arch. f. klin. Chir.*, 1925: 137: 731. — WIEDERHOFER: quoted by BROCHINGTON & LIGHTWOOD.

Genu Varum in Children: Typical Roentgen Picture.

By

AXEL RENANDER.

The commonest cause of both bowleg and knock-knee in children is rickets. The roentgen diagnosis of these cases is generally a simple matter, in view of the characteristic changes to be found in the epiphyses of other long bones also. The deformities may also arise through local morbid processes near the epiphyseal lines. Partial destruction of the epiphyseal cartilage then leads to asymmetrical longitudinal growth with curvature of the leg as a result. The roentgenologic diagnosis of these cases, too, is relatively easy.

In addition to these generally known types of deformity of the knee joint, the literature contains a few reports of cases of genu varum in children, all of which showed the same complicated roentgen characteristics. The first of these was described by MAU in 1924. Later, NILSONNE and BARBER each contributed one case. The roentgen pictures in these three cases are strikingly similar.

Characteristic of the roentgen findings in these cases was that the proximal tibial epiphysis was lower medially than normal and wedge-shaped. Under it there was an exostosis issuing from the medial aspect of the tibial metaphysis, resembling either a beak or a bracket. The bone structure in both the epiphysis and the metaphysis was mostly irregular with a number of areas of rarefaction alternating with coarse trabeculae. The epiphyseal line was not increased in breadth, but usually was irregular and wavy. In none of these cases could any rachitic changes be demonstrated.

The clinical findings also were characteristic. Palpation revealed a hollow corresponding to the medial tibial epiphysis. An exostosis could be palpated just below the hollow at the site of the medial aspect of the metaphysis.

The interpretation of the roentgenograms in these cases was difficult. MAU considered that the deformity should be considered as due to the development of a cartilaginous exostosis on the medial aspect of the tibial metaphysis. This theory undoubtedly finds support in BARBER's claim that he had found islands of cartilage in the exostosis. These islands of cartilage, BARBER believed, were visualized at the rounded areas of rarefaction in the exostosis. NILSONNE was somewhat skeptical as to the accuracy of this interpretation, particularly in view of the fact that cartilaginous exostoses could not be demonstrated in other places and also in view of the general appearance of the tibial exostoses. He suggested, instead, the possibility of a growth disturbance comparable with osteochondritis deformans juvenilis, but he left open the question of etiology. BARBER named the disease osteochondrosis deformans tibiae, pointing out that it had no connection with rickets. However, he did not discuss the etiology in any detail. So far, the problem of etiology does not seem to have been solved.

NILSONNE and especially MAU both found similarities between their cases and a case reported by VALENTIN. As far as I can see, the resemblance was confined to external appearance and to some extent to the fact that medially the tibial epiphysis was somewhat lower than normal. For the rest, VALENTIN's case differed from the others in one important respect: the epiphyseal line showed a considerable increase in breadth and the borders of the temporary calcific zone were very irregular and, as far as can be judged from the reproductions of the roentgenograms, partly obliterated. In my opinion, VALENTIN's case most closely resembled an advanced case of rickets.

A boy of two and a half years was admitted to the Pediatric Ward of Centrallasarettet on August 17, 1944, for pronounced bowleg.



Fig. 1.

The patient's parents and half-siblings were healthy. One sibling was mentally deficient following a cerebral hemorrhage at the age of eleven months. There was no bowleg in the family.

The patient was born at term. Like all his siblings, he was small at birth, weighing only 2 400 Gm. He was breast-fed until three months, after which he was given cow's milk only, in formulas prescribed by the local Child Health Center. He was given codliver oil in the winter of 1942—43 and Solesan, a proprietary vitamin tonic, in the winter of 1943—44. During the summers he was out of doors for several hours a day.

The patient sat up at five to six months, walked at thirteen months. His first tooth erupted at four months, and he had about eight teeth at one year.

When the patient was about nine or ten months old, his family noticed that he seemed unusually bow-legged. The deformity increased when he began to walk. It was most pronounced during the winter of 1943—44, but improved somewhat in the following spring and summer, the left leg in particular becoming straighter.

On admission the patient's general condition was good. He was 89 cm long (normal length for age: 86.7 to 106.7 cm) and weighed 13.97 kg (normal weight for age: 11.2 to 15.7 kg). His colour was good, and he was well nourished. The throat, tongue and thyroid were nor-



Fig. 2.

mal. He had 8/10 faultless teeth. Heart examination: the beat was not palpable; the borders were normal; there was a systolic murmur over the whole heart, most pronounced at the base. The lungs and abdomen were normal. The liver and spleen were not palpable. The genitals were normal. The skeleton and shape of the head were normal. The head measured 50.5 cm in circumference, and the fontanel was closed. The chest measured 53.5 cm in circumference and was normally shaped. The cartilaginous margins were somewhat more prominent than usual, but nothing definitely pathologic could be noted. The spine, arms, wrists and hands were normal. There was pronounced genu vara (Fig. 1), with a distance of six centimeters between the inner contours of the knees when the feet were together.

Roentgen examination of the knees (Figs. 2 and 3) revealed the general calcium content to be normal. The epiphyseal line in the proximal tibial epiphysis was sharply outlined, but somewhat wavy.

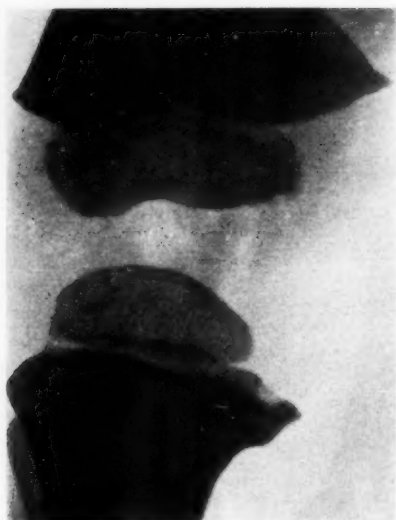


Fig. 3.

The temporary calcific zone of normal thickness in the epiphysis; on the metaphysis side it was somewhat thickened, especially medially. At this point the metaphysis showed a bracket-like projection. The bone structure in the projection was partly sclerotic and partly irregular, due to areas of rarefaction in the sclerotic tissue. The epiphysis was perhaps slightly lower than normal medially, but its bone structure was normal.

The femur also exhibited suggested changes of the same kind. The epiphyseal line was somewhat broader than normal medially, and the zone of temporary calcification on the metaphysis side was thickened and sclerotic medially. The metaphysis projected in a point medially.

This case corresponded with those described by MAU, NILSSONNE and BARBER with regard to the changes in the head of the tibia. In addition it showed the same changes in the distal end of the femur as BARBER's case.

My case also fails to make any positive contribution to the etiology. As in the other cases, rickets could be disregarded as a possible cause of the deformity. Neither the clinical nor the

roentgenologic examination revealed any signs of rickets, even though the deformity was clinically reminiscent of a postrachitic change.

Summary.

A report is given of a case of genu varum in a child with characteristic changes in the epiphyseal cartilage and neighbouring metaphyses of the tibia and the femur.

References.

BARBER, C. G.: Osteochondrosis Deformans Tibiae: Nonrachitic Bowleg in Children. *Am. Journ. Dis. Child.* 64: 831—842. 1942. *Ref. Year Book of Radiology* 1943. (The Year Book Publishers, Inc. Chicago.) — MAU, C.: Genu varum bedingt durch Tibiaepiphysendefekt bei kartilaginärer Exostose. *Zeitschr. f. orthop. Chir.* Bd. XLIV. 1924. S. 383. — NILSSONNE, H.: Genu varum mit eigentümlichen Epiphysenveränderungen. *Acta Chir. Scand.* Vol. LXIV. 1929. S. 187. — VALENTIN, B.: Über eine eigenartige, bisher unbekannte Form multipler Epiphysenstörungen. *Fortschr. a. d. Geb. d. Röntgenstrahl.* Bd. 20. 1922. S. 120.

Über Höckerbildung in den Schädelknochen bei schweren Anaemien der Kinder.

Zwei Fälle von Anaemia haemolytica mit 4 Bildern.

Von

VUOKKO LIAKKA.

Knochenveränderungen, die im Verein mit Erkrankungen des Blutes bei Kindern in Erscheinung treten, finden wir im Schrifttum nicht gerade häufig erwähnt. Man trifft eigentlich nur Angaben über das regelmässige Vorkommen von Veränderungen im Knochensystem bei der in den Mittelmeerländern heimischen s. g. COOLEY'schen Anaemie, die besonders in Verdickungen der Schädelknochen zu Tage treten sollen. SPILIPULOS und CHOREMININ machen geltend, dass derartige Veränderungen durchaus nicht nur für die COOLEY'sche Anaemie spezifisch sind, sondern dass man sie mitunter auch bei andern sekundären Anaemien, wie bei Malaria, Syphilis und haemolytischem Ikterus antrifft.

Das sogen. Caput quadratum der Kinder, für welches eckige, höckerig verdickte Stirn- und Scheitelbeine charakteristisch sind, ist früher immer nur als ein Produkt von rachitischen Knochenprozessen angesehen worden. YLPPÖ hat jedoch im Zusammenhang mit seinen pathologisch-anatomischen Studien über Frühgeburten festgestellt, dass diese Höckerbildung in den Schädelknochen überhaupt erst in Verein mit einer Anaemie zur Entwicklung kommt; er hat auch dargetan, dass diese Verdickungen der Schädelknochen ihren Ursprung hauptsächlich in einer lebhafteren Tätigkeit der blutbildenden Organe haben. In YLPPÖ's Fällen erschien das Knochengewebe in den Schädelhöckern überwiegend als ein stark hyperplastisches Gewebe und die zwischen den

Knochenbalken und Lamellen befindlichen Lücken waren angefüllt von zahlreichen roten und verschiedenartigen weissen Blutkörperchen. Bei den Frühgeburten-Anaemien tritt also im Mark nicht nur der Röhrenknochen, sondern auch der flachen Knochen (Schädelknochen) eine Hyperfunktion in der Blutbildung in Erscheinung, welche dann auch die eben erwähnte Hyperplasie des Knochenmarkes zur Folge hat. Die Entstehung der Scheitelbeinhöcker leitet YLPPÖ von der primären Hyperplasie des Knochenmarkes her, welche ihrerseits durch ihre Reizwirkung sowohl zu einer kräftigern Resorption des Knochengewebes als gleichzeitig auch zu lebhafterer Neubildung von Osteoidgewebe führt. Als Endprodukte dieses lebhaften proliferativen und resorptiven Knochen- und Knochenmarks-Bildungsprozesses entstehen dann die erwähnten Knochenhöcker.

VOGT und DIAMOND haben 19 chronische Anaemien mit Veränderungen in den Knochen veröffentlicht. 5 von ihnen gehörten zur Gruppe des haemolytischen Ikterus, 1 war eine Neger Sichel-Zellanaemie und 13 gehörten zu den den Mittelmeerrassen eigenen Etythroblasten-Anaemien. Bei allen diesen war die Hyperaktivität des Knochenmarkes in den Knochen der Gliedmassen, in den Rippen-, Metakarpal- und Tarsalknochen aufgetreten. SHELING und BRAUN haben (1930) einen Fall von haemolytischem Ikterus bei einem 6-jährigen Mädchen bekanntgegeben, wo neben den klinischen Symptomen auch Veränderungen in der Struktur des Knochengewebes röntgenologisch nachweisbar waren. Die Schädelaufnahme zeigte eine verdickte tabula externa wie auch Veränderungen in der Diploe. Sowohl in den langen wie auch in den kurzen Knochen waren zystenartige Aufhellungen zu erkennen. ACUNA MAMERTO hat (1938) Mitteilung über zwei Fälle von haemolytischem Ikterus gemacht, bei denen bedeutende Knochenveränderungen vorhanden waren, das Mark war verbreitert, die Corticalis verschmälert und porös und die Trabekelbildung unregelmässig.

Der von mir vorgestellte Fall, Eira M., Tochter eines Kleingrundbesitzers, das zweite Kind, befand sich in Behandlung auf der Station für Kinderkrankheiten des Allgemeinen Krankenhauses zu Helsinki vom 4/2—25/8 1944. Bei Aufnahme ins Krankenhaus war sie 13 Jahre 10

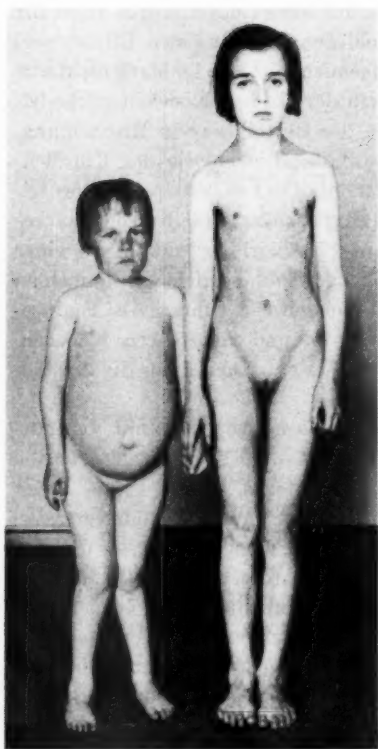


Bild 1.

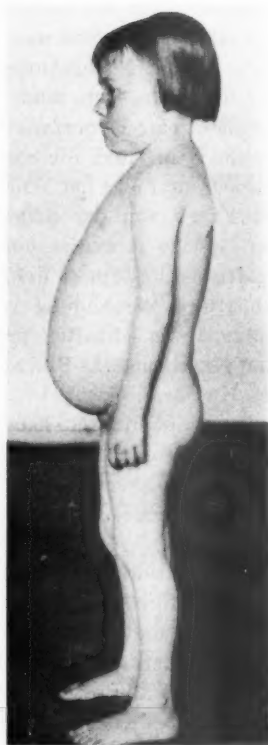


Bild 2.

Mon. alt. Ihr Vater war bei 36 Jahren im Jahre 1942 an Magengeschwür gestorben, die Mutter ist gesund. Von 4 Kindern sind die übrigen Geschwister gesund. Bei niemandem in der Verwandtschaft ist Gelbfärbung beobachtet worden. Ihr Gewicht bei der Geburt war 3 200 gr. Das Befinden gleich nach der Geburt war gut. Aufzusitzen begann sie im Alter von 1/2 Jahr, erste Gehversuche machte sie als etwa 1-jährig; zur selben Zeit fing sie an zu sprechen. Die Zahnung ging zu den gewöhnlichen Terminen vor sich. Brustmilch erhielt Pat. im Laufe von 2 Jahren. War von klein auf schwächer als die andern Kinder. Esslust ist immer schlecht gewesen. Ist beständig blass gewesen. Das



Bild 3.

Wachstum machte nur langsam Fortschritte, sie verblieb auch mager, bloss der Bauch wölbte sich vor. Häufige Durchfälle. Patientin ist nicht bettlägerig gewesen, hat sich auch draussen aufgehalten, ermüdete dabei aber leicht und bekam Herzklopfen und Atemnot sobald sie sich etwas stärker bewegte. Temperatursteigerungen sind nicht bemerkt worden; sie hat auch nicht gehustet. Wegen ihrer schwachen Gesundheit hat sie die Schule nicht besuchen können, sondern hat Lesen und Schreiben zuhause gelernt.

Mit 3 Jahren hat Pat. den Keuchhusten durchgemacht; keine andern Infektionskrankheiten gehabt. Ist wegen ihrer Kränklichkeit nicht gegen Pocken vakziniert worden. Bei 5 Jahren sind bei ihr Bandwürmer festgestellt worden und ist Pat. einer Bandwurmkur unterzogen worden. Die Menstruation hat sich noch nicht eingestellt und geschlechtlich ist sie noch vollständig unentwickelt.

Patientin ist für ihr Alter von auffallend kleinem Wuchs, Länge 110,5 cm., das subkutane Fettgewebe mässig entwickelt, an den Bauchdecken ist es doch recht reichlich vorhanden, das Körpergewicht 21 800 gr.



Bild 4.

Siehe das Bild: Neben ihr stehend ein 12-jähriges Mädchen. Die Muskulatur ist schwach entwickelt.

Hautfarbe blass, Schleimbäute anaemisch. Skleren leicht ikterisch.

Knochengerüst: Umfang des Kopfes 52 cm., Brustumfang 63 cm. In der Medianlinie des Kopfes eine vom Scheitel zum Hinterkopf verlaufende Furche, die dadurch zustande kommt, dass die Tubera frontalia und parietalia bedeutend vergrößert sind und vorragen (Caput quadratum). Siehe die Bilder. Die Form des Brustkorbes wie gewöhnlich, kein Rosenkranz, leicht angedeutete Harrison'sche Furche. Die Extremitätenknochen normal, keine Epiphysenverdickungen. Das Rückgrat ohne Verkrümmungen. Mehrere schadhafte Zähne.

Nervensystem: Nichts besonderes.

Atmungsorgane: Nichts besonderes.

Kreislauforgane: Puls regelmässig, von gleichmässiger Qualität, 116/Min. Blutdruck 95/40 mm. Hg. Die relative Herzdämpfung erstreckt sich nach links bis zur Mammillarlinie, rechts 1 Querfinger nach aussen vom rechten Sternalbende. Spitzenstoss im V. Inter-

28/IV. 44.

Gewicht 24,6 kg.

Glykose 49,2 g.

						Blutzucker
Vor Darreichung der Glykose						0,110 %
5 Min. nach Darreichung der Glykose						0,140 »
15	»	»	»	»	»	0,150 »
30	»	»	»	»	»	0,200 »
45	»	»	»	»	»	0,155 »
1 St.	»	»	»	»	»	1,150 »
1 1/2	»	»	»	»	»	0,150 »
2	»	»	»	»	»	0,160 »
2 1/2	»	»	»	»	»	0,160 »

3/V. 44.

Gewicht 25,2 kg.

Glykose 50,4 g.

						Blutzucker
Vor Darreichung der Glykose						0,140 %
5 Min. nach Darreichung der Glykose						0,160 »
15	»	»	»	»	»	0,170 »
30	»	»	»	»	»	0,180 »
45	»	»	»	»	»	0,180 »
1 St.	»	»	»	»	»	0,180 »
1 1/2	»	»	»	»	»	0,150 »
2	»	»	»	»	»	0,140 »
2 1/2	»	»	»	»	»	0,150 »

Die ersten 3 Wochen nach Aufnahme ins Krankenhaus fieberte Patientin zwischen 37°—38° morgens und 38°—39° abends.

Patienten lag zu Bett, tagsüber draussen in der Halle, erhielt Eisen und Leber. Allmählich bekommt Patientin frischeres Aussehen, der Allgemeinzustand bessert sich, die Temperatur fällt zur Norm ab. Die Skleren bleiben allerdings die ganze Zeit subikterisch. Die Leber und Milz sind kleiner geworden. Das Blutbild hat sich gebessert.

16/3. Blutbild: Hgb: 36/45 %, Erythrozyten 3,39 Mill. I. 0,66 Leukozyten 4900. Differ: Neutrophile stabkern. 2,0, segmentkern. 52,5. Eosinophile 1,5, Basophile 1,5, Monozyten 2,8, Lymphozyten 40,0, Thrombozyten 212 800.

Der Zustand verblieb darauf 3 Monate ziemlich unverändert. Die Skleren erschienen zeitweise stärker ikterisch. Von Zeit zu Zeit zeigten sich auch kleine Temperatursteigerungen, wobei dann auch die Milz etwas vergrößert zu sein schien. Das Blutbild verblieb einigermassen unverändert.

Auf eine Splenektomie wollten sich die Chirurgen nicht einlassen, da der Fall durch innersekretorisch bedingte Wachstumsstörungen,

Skelettveränderungen und positive Kahn-Reaktion kompliziert war. Dem letztgenannten Umstand hätte man allerdings bei diesem ikterischen Kinde keine grössere Bedeutung beizulegen gebraucht, besonders da die *Wassermann-Reaktion* absolut negativ war.

Da der Zustand sich auch weiterhin stationär hielt, wurde am 17./6. der Versuch mit einer Bluttransfusion gemacht. Patientin erhielt dabei direkt vom Spender 250 cem. 0-Blut und fühlte sich unmittelbar nach der Blutübertragung ganz besonders gut. Die Erholung war in die Augen fallend. Hgb. stieg von 33/41 % auf 42/52 %, die Zahl der roten Blutkörperchen von 2,97 Mill. auf 3,42 Mill.

Der Zustand der Patientin blieb dann den ganzen Sommer über einermassen gut und sie war fieberfrei. Sie hielt sich viel draussen auf, brannte ein und der Appetit besserte sich. Da diese Blutübertragung einen sichtbaren Nutzen zur Folge gehabt zu haben schien, wurde am 25./7. 44 ein neuer Versuch unternommen, wobei Patientin wieder 250 cem. 0-Blut erhielt. Unmittelbar nach der Übertragung hatte Patientin dieses Mal eine vorübergehende Temperatursteigerung und leichtes Üblichkeitsgefühl. Der Haemoglobingehalt stieg ein wenig, von 48/60 % auf 52/65 %, die Zahl der roten Blutkörperchen jedoch verblieb ungefähr dieselbe, 4,4 Mill. Darauf verharrte der Zustand im Laufe eines Monats im übrigen ziemlich auf derselben Stufe, nur mit der Ausnahme, dass die Menge der roten Blutkörperchen ein wenig abnahm, indem sie von 4,42 Mill. auf 3,91 Mill. sank, wobei der Haemoglobingehalt jedoch sich stationär hielt. Da Patientin nach den vorhergehenden Blutübertragungen sich zusehends erholt hatte, wurden ihr wieder am 24./8. 44 200 cem. 0-(Citrat) Blut intravenös verabreicht. Nach dieser Transfusion war die Entlassung des Mädchens nach hause in Aussicht genommen. Unmittelbar nach der Blutübertragung gutes Befinden, doch traten nach 3 Stunden leichte Übelkeit und nach 4 Stunden ein Collaps ein, von dem sich Patientin, ungeachtet vielfacher Massnahmen, nicht mehr erholte. 12 Stunden nach der Blutübertragung trat der Tod ein.

Obduktion: Kopf: Schädelknochen besonders dick, vorzugsweise in Gegend der Scheitelbein- und Stirnbeinhöcker, misst an der dicksten Stelle 2,5 cm. Gehirnoberfläche glatt, Windungen wie gewöhnlich, Gehirnventrikel normal, Gehirngewebe wie gewöhnlich.

Die Brusthöhle enthält dunkle, gelbgefärbte Flüssigkeit, Lungenkonsistenz normal. Lungen überall lufthaltig, Probestücke schwimmen auf dem Wasser. Im Herzbeutel reichlich ein Esslöffel Flüssigkeit. Das Herz von der Grösse der Faust einer kleinen Frauensperson. Endokard und Klappen glatt. Herzmuskel wie gewöhnlich.

In den Bauchdecken ein reichliches Fettlager. Wo im Körper man auch auf Fett- oder Bindegewebe stösst, überall haben diese eine stark gelbe Färbung. In der Bauchhöhle eine beträchtliche Menge gelber Flüssigkeit. Die Leber ist gross und drängt das Zwerchfell nach oben,

wodurch das Volumen der Brusthöhle unverhältnismässig eng erscheint. Die Konsistenz der Leber ist fester als gewöhnlich. An der Schnittfläche ist Bindegewebe in punktförmiger Anordnung festzustellen. Die Milz ist gross, ihr Gewicht 320 g., an der Schnittfläche ist das Blut geronnen, die Struktur verwischt.

Magen und Darm von gewöhnlichem Aussehen. An der Oberfläche des Dünndarmes sind die Venen breiter als gewöhnlich. Das Netz geschwollen, bedeutend dicker als gewöhnlich, das Mesenterium hat dasselbe verdickte Aussehen. Bauchspeicheldrüse normal. Nieren von gewöhnlicher Grösse und Form, ihre Struktur deutlich zu erkennen. Nierenbecken wie gewöhnlich, ihre Schleimhaut glatt.

Die *mikroskopische* Untersuchung ergab, dass das Lebergewebe zirrhotisch verändert ist; stellenweise hat der Schwund des Leberparenchyms mehr an der Peripherie des Lobulus stattgefunden, an andern Stellen ist dieser Vorgang ziemlich gleichmässig über den ganzen Lobulus verteilt. An diesen Stellen ist stattdessen ein feines fibrilläres Bindegewebe aufgetreten. Es hat also den Anschein, dass es sich hier entweder um eine glatte zirrhotische Atrophie oder eine dem ähnliche Zirrhosenbildung in der Leber handelt. Die Kupfer'schen Sternzellen sind hypertrophisch, Pigment tritt dagegen in der Leber nicht in eben nennenswerter Menge auf.

In der Milz erscheint wiederum das retikuläre Gewebe stark hyperplastisch und hypertrophisch, doch erscheint auch hier Pigment nur in kaum nennenswerter Menge. Das lymphatische Gewebe ist verhältnismässig nur spärlich vertreten. Das histologische Bild weist also auf einen RetikULOseprozess der Milz hin.

Im Brustbeinpraeparat war hyaliner Knorpel, spongiöser Knochen und schliesslich Knochenmark in hyperplastischem Zustande anzutreffen.

In dem dem Schädel entnommenen Praeparat ist spongiöser Knochen mit Markinhalt zu erkennen. Über die Beschaffenheit dieses letzteren lässt sich an dem durch Dekalzinierung hergestellten Praeparat keine sichere Diagnose stellen, wenngleich man doch den Eindruck gewinnt, dass es auch hyperplastisch ist.

Die in Frage stehende Patientin war also ein in Bezug auf ihr Alter im Wuchs stark zurückgebliebenes, ihrer Intelligenz nach aber vollständig normales Mädchen, an dem in erster Linie die Blässe, die subkterischen Skleren und die ganz geringe gelbliche Schattierung der Haut, der grosse Bauch und die eigenartige viereckige Form des Kopfes mit den grossen Stirnbein- und Scheitelbeinhöckern in die Augen fielen. Der Zustand war von chronischer Natur, indem sich sein Beginn bis in die aller früheste

Kindheit verfolgen lässt; das Kind ist jedenfalls nachweislich schon im Alter von 2 Jahren als krank angesehen worden, ohne dass aber die Angehörigen über etwas anderes als Müdigkeit, Blässe und schwache Entwicklung der Patientin zu klagen verstanden. Bei eingehenderer Untersuchung wurden die Vergrößerung der Leber und der Milz aufgedeckt, die stark ausgeprägte sekundäre Anaemie, die Anisozytose, Poikilozytose und Mikrozytose nachgewiesen, wie auch die herabgesetzte Resistenz der roten Blutkörperchen festgestellt. Die Sternalpunktion ergab ein zellreiches, erythropoetisches Mark. Meulengracht war erhöht. Im Urin konnten Gallenfarbstoffe nachgewiesen werden. Im Blut erhöhter Meulengracht-Wert. Die Lungen waren gesund ebenso wie auch am Herzen nichts anderes als ein anaemisches Geräusch festzustellen war. Die Röntgenaufnahme des Schädels zeigte in der Gegend der Schädelhöcker starke Verdickung der Schädelknochen.

Es hat sich hier also offenbar um einen auf kongenitaler Grundlage entstandenen haemolytischen Ikterus gehandelt; zu dessen Krankheitsbild gesellten sich stark ausgeprägte Skelettveränderungen am Schädel, Höckerbildungen im Stirn- und in den Scheitelbeinen; dazu kam noch eine bedeutende Wachstumsstörung. Im Laufe der letzten Jahre sind auf der Kinderklinik vier andere Ikterus haemolyticus-Fälle in Behandlung gewesen, von denen bei zweien ganz entsprechende grosse Höckerbildungen in den Schädelknochen festgestellt wurden. Nach der in diesen Fällen in Erscheinung tretenden Hyperplasie des Markes zu urteilen, regt die kongenitale anaemisierende und haemolysierende Noxe bei Kindern auch das Knochenmark der Schädelknochen zu blutbildender Tätigkeit an, und dieser Umstand seinerseits dient, wie YLPPÖ es bei den Frühgeburten-Anaemien nachgewiesen hat, als Reiz für eine kräftigere Knochenneubildung. Da diese Knochenhöcker vorzugsweise bei den Frühgeburten-Anaemien aufzutreten pflegen und als so imponierend auch bei den in Frage stehenden haemolytischen Anaemien vorkommen können, bei denen die anaemisierende Noxe auch schon kongenital in Wirkung getreten ist, liegt der Gedanke nahe, dass im Säuglingsalter das Knochengewebe auf die auch in den Schädelknochen sich entwickelnde Hyperfunktion des Markes äusserst sensibel mit zunehmender Osteoid-Produktion

reagiert, und dass daher die Schädelhöcker, obgleich sie in diesen Fällen im selben Alter zu Tage treten wie die rachitischen Knochenveränderungen, doch nichts mit Rachitis zu tun zu haben brauchen.

Zusammenfassung.

Bei schweren anaemischen Zuständen bei Kindern trifft man manchmal besonders starke, höckerartige Verdickungen in den Schädelknochen, speziell in den Scheitelbeinen (übertriebenes Caput quadratum). Ein schwerer Fall von Anaemia haemolytica bei einem 13-jährigen Mädchen wird genauer beschrieben.¹

Diese Knochenhöcker sind — wie YLPPÖ es bei seinen Studien über Frühgeburten dargetan hat — als Produkte einer Reaktion des Knochengewebes auf infolge krankhafter Blutneubildung im Knochenmark entstehende Reize anzusehen.

Literatur.

ACUÑA, MAMERTO: Röntgenologisch nachweisbare Störungen des Skeletts beim angeborenen hämolytischen Ikterus. Arch. argent. Pediatr. 9, 99 108 1938 (Spanisch) Ref. Zentr. Bl. für Kinderh. XXXVI, S. 122. — CHOREMIS, K. SPILIPULOS, G.: Über die Ätiologie und Therapie der Cooleyschen Anämie. Jb. Kinderheilk. 148, 317—328 (1937). — COOLEY, THOMAS B., E.-R. WIKNER and PEARL LEE: Anemie in children with Splenomegaly and peculiar changes in the bones. Report of cases. Amer. J. of dis. of children Bd 34 no 3, 347—363 (1927). — LEONE, A. and E. LUGAS: Sulla anemia eritroblastica con osteoporose (Sindrome di Cooley) Clin. pediatr. 18, 467—515, 1936. — SNELLING, CHARLES E. and ALAN BROWN: A case of hemolytic jaundice with bone changes. J. Pediatr. 8, 330—377 (1936). — VOGT, EDWARD C. and LOUIS K. DIAMOND: Congenital anemias, roentgenologically considered. Amer. J. Roentgenol. 23, 625—270 (1930). — YLPPÖ: Pathologisch-anatomische Studien bei Frühgeborenen. Ztschr. f. Kind. XIX. H. 1—2, 1918.

¹ Bei der Drucklegung ist in der Universitäts Kinderklinik zu Helsinki ein ganz gleichartiger Fall von Anaemia haemolytica aufgenommen. Der Patient, ein 13-jähriger Knabe, hat ähnlichen infantilen kurzen Körperbau, die typischen Höckerbildungen in den Schädelknochen und eine stark vergrößerte Milz, typische Coxa vara und Genu valgum. Geistig normal. Das Blutbild: Hgb. 34/43. Erythro. 2,45 milj. Leuko. 4 400. I: 0,99. Poikelozyt. +. Anisozyt. +. Beginn der Haemolyse bei 0,68 % NaCl, komplett bei 0,24 % NaCl. WaR —. Kahn —. Meulengracht 1:15.



ACTA PÆDIATRICA

EDITORES:

A. LICHTENSTEIN, STOCKHOLM, A. WALLGREN, STOCKHOLM

REDACTORES:

IN DANIA: BENT ANDERSEN, AARHUS, OLUF ANDERSEN, KØBENHAVN, C. E. BLOCH, KØBENHAVN, P. PLUM, KØBENHAVN. *IN FENNIA:* P. HEINIÖ, HELSINGFORS, V. RANTASALO, HELSINGFORS, C. E. RÄIHÄ, HELSINGFORS, T. SALMI, ÅBO, ARVO YLPPÖ, HELSINGFORS. *IN HOLLANDIA:* E. GORTER, LEIDEN, CORNELIA DE LANGE, AMSTERDAM, J. VAN LOOKEREN CAMPAGNE, GRONINGEN. *IN NORVEGIA:* TH. FRÖLICH, OSLO, LEIF SALOMONSEN, OSLO, L. STOLTENBERG, OSLO, A. SUNDAL, OSLO, KIRSTEN UTHEIM-TOVERUD, OSLO. *IN SUECIA:* C. GYLLENSWÄRD, UPPSALA, N. MALMBERG, STOCKHOLM, STURE SIWE, LUND, WILHELM WERNSTEDT, STOCKHOLM, Y. ÅKERRÉN, GÖTEBORG.

REDIGENDA CURAVIT

A. LICHTENSTEIN

KRONPRINSESSAN LOVISAS BARNSJUKHUS,
STOCKHOLM

Vol. XXXIII. Fasc. 2

31: VI. 1946

Almqvist & Wiksells Boktryckeri Aktiebolag
UPPSALA 1946

ACTA PÆDIATRICA

PROFESSOR A. LICHTENSTEIN
KRONPRINSESSAN LOVISAS BARNSJUKHUS,
30 POLHEMSGATAN, STOCKHOLM

The 'ACTA PÆDIATRICA' contain articles relating to pediatrics. These articles are published in English, French or German, according to the wishes of the author. Each number consists of about 6 printed sheets, 4 numbers forming a volume. The numbers will be issued as soon as the articles sent in can be printed. The 'Acta' is open to articles from foreign authors in all countries, if sufficient space can be found for them. Manuscripts are to be sent direct to the Editor, to whom also enquiries about the exchanging of papers are to be directed. The subscription should be forwarded to the Editor. Each volume costs 25 Swedish crowns or 25 shillings or 5 dollars.

ACTA PÆDIATRICA enthalten Arbeiten aus dem Gebiete der Kinderheilkunde. Die Arbeiten werden, je nach eigener Wahl des Verfassers, in deutscher, französischer oder englischer Sprache veröffentlicht. Jedes Heft enthält circa 6 Druckbogen; 4 Hefte bilden einen Band. Die Hefte erscheinen, je nachdem die in dieselben aufzunehmenden Aufsätze druckfertig vorliegen. Die Acta nehmen nach Möglichkeit auch Arbeiten ausländischer Verfasser aller Nationen auf. Manuskripte nimmt der Herausgeber entgegen, desgleichen Wünsche betreffs Austausch von Zeitschriften. Abonnementanmeldung bei dem Herausgeber. Preis pro Band 25 schwedische Kronen.

Les ACTA PÆDIATRICA contiennent des ouvrages du domaine de la pédiatrie. Les études sont publiées en français, anglais ou allemand au choix de l'auteur. Chaque fascicule contient env. 6 feuilles in-8°; 4 fascicules forment un volume. Les fascicules paraissent au fur et à mesure que les articles y destinés sont imprimés. Les Acta reproduisent, dans la mesure du possible, les articles d'auteurs étrangers de tous les pays. Les manuscrits doivent être expédiés à l'éditeur, à qui les demandes relativement à l'échange de journaux devront également être adressées. Abonnement chez l'éditeur. Prix par volume Cr. Suéd. 25.

ACTA PÆDIATRICA





ISAK JUNDELL





ISAK JUNDELL

1867—1945

Am Abend des vergangenen ersten Weihnachtsfeiertages (25.12.1945) starb im Alter von 78 Jahren Professor emeritus ISAK JUNDELL in seinem Heim in Stockholm. Mit ihm erlosch eine Lebensflamme, die während Jahrzehnten mit starkem Schein in unseren pädiatrischen Kreisen geleuchtet hatte.

ISAK JUNDELL hatte sich ursprünglich nicht die Kinderheilkunde als Lebensziel gedacht. Die ersten Jahre nach bestand-nem medizinischen Examen beschäftigte er sich hauptsächlich mit der Bakteriologie. 1898 wurde er Dozent der inneren Medizin und 1907 Oberarzt am provisorischen Krankenhaus Stockholms.

Bereits vorher hatte sich jedoch JUNDELLS Interesse seiner endgültigen Lebensaufgabe zugewandt. Um 1900 finden wir ihn als Unterarzt bei MEDIN am Allgemeinen Kinderhause (Allmänna Barnhuset), — eine Einrichtung, die später vor allem durch ihn von Grund auf umgestaltet werden sollte. Im Jahre 1905 tauschte JUNDELL seine Dozentur der inneren Medizin gegen eine Dozentur der Pädiatrie um. Nach weiterer Ausbildung im Ausland, vor allem an FINKELSTEINS Klinik in Berlin, war JUNDELL gerüstet, mit Erfolg den Kampf um die nach MEDIN 1912 frei gewordene Professur der Pädiatrie am Karolinischen Institut aufzunehmen. Er wurde 1914 zum Nachfolger MEDINS und gleichzeitig zum Oberarzt an »Allmänna Barnhuset« ernannt.

Für JUNDELL begann jetzt eine Zeit mühevoller Arbeit, um bessere Unterrichtsmöglichkeiten für die Medizinstudenten und auch bessere Formen für die soziale Kinderpflege zu schaffen.

Er öffnete neue Wege für den Schutz alleinstehender Kinder und ihrer Mütter. Die alte Wirksamkeit von »Allmänna Barnhuset» wurde langsam abgewickelt. Das alte Einlösungssystem wurde schliesslich praktisch genommen ganz gegen eine soziale Kinderpflege nach modernen Grundsätzen ausgetauscht. Die für Waisenkinder eingerichteten Säle leerten sich mehr und mehr, und es wurde Platz frei für die ständig höher werdende Anzahl kranker Kinder. So bekam die Anstalt mehr und mehr den Charakter eines wirklichen Kinderkrankenhauses. Als Krankenhaus wurde der ganze Waisenhauskomplex beim Abgang JUNDELLS von seiner Professur 1932 von der Stadt Stockholm übernommen und der Name in »Krankenhaus Norrtull» geändert.

JUNDELL war in allen Gebieten der Kinderheilkunde interessiert und aktiv. Sowohl wissenschaftliche Forschung und Unterricht als auch die soziale Kinderpflege lagen ihm warm am Herzen. Selbst ist er verschiedentlich als Forscher hervorgetreten. Aus der ersten Zeit stammen hauptsächlich Untersuchungen über eine Reihe Infektionskrankheiten und auf dem Gebiete der inneren Medizin. Erst Anfang des Jahrhunderts legt JUNDELL seine ersten rein pädiatrischen Studien vor — die vorbildlich durchgeführten, grundlegenden Untersuchungen über die Variationen der Körpertemperatur beim Säugling. Bei seinen folgenden pädiatrischen Arbeiten wendet er oft die Bakteriologie als Hilfswissenschaft an. So wurden vor allem Scharlach und die Calmettevaccination Gegenstand seines Interesses. Beachtungswerte Einsätze hat JUNDELL auch durch seine Arbeiten über »Untersuchungen über den Stoffwechsel bei der Dyspepsie und der alimentären Intoxikation», über die Rachitis, gemischte Kost bei Säuglingen und mehrere andere Themen gemacht. Auch mit Erziehungsfragen und der Popularisierung seiner Wissenschaft beschäftigte er sich gern.

Die grösste Bedeutung JUNDELLS liegt jedoch auf anderem Gebiet. Keiner dürfte wohl in unserem Land seit HENRIK THEODOR BERGS Tagen so energisch und mit solchem Erfolg wie JUNDELL für die praktische Reform sowohl im pädiatrischen Unterricht als auch in der sozialen Kinderpflege eingetreten sein.

Zu den grossen Verdiensten JUNDELLS gehören auch die mit

Hilfe des Nordischen Hausmütterverbandes 1923 durchgeführten Ausbildungskurse für Kinderkrankenschwestern — »Jundellare» — an »Allmänna Barnhuset». Hiermit legte JUNDELL den Grund zur Spezialausbildung von Kinderkrankenschwestern, die jetzt der Staat übernommen hat, und die weiterhin im grossen und ganzen nach den Richtlinien JUNDELLS geführt wird.

Ein kennzeichnender Zug bei JUNDELL war sein wacher Sinn für die Bedeutung internationaler Verbindungen zwischen den Kinderärzten. JUNDELL war zwar nicht unter den Gründern der Nordischen Pädiatrischen Vereinigung; aber es war JUNDELLS Initiative zu verdanken, dass 1921 das zusammenhaltende Organ und Sprachrohr dieser Kreise nach aussen, die »Acta pädiatrica» entstand. Von Anfang an hat auch die Arbeit als Hauptredakteur und verantwortlicher Herausgeber in seinen niemals ermüdenden Händen gelegen.

Das Streben JUNDELLS nach Zusammenhalten und Zusammenarbeit unter den Pädiatrikern streckte sich doch weit über die nordischen Staaten hinaus. Als sich die Wellen der Leidenschaften nach dem ersten Weltkriege allmählich gelegt hatten, nahm JUNDELL mit den leitenden Pädiatrikern der Kulturländer die Verbindung auf. Es lag ihm am Herzen, die 1912 in Paris begonnene internationale pädiatrische Zusammenarbeit wenn möglich wieder in Gang zu bringen. Mit der ihm eigenen zähen Energie und grossem Zielbewusstsein überwand er alle Hindernisse — sie waren nicht unbedeutend —, die sich ihm in den Weg stellten. So war es in erster Linie JUNDELLS Verdienst, dass die Pädiatriker aller Länder zu friedlicher Zusammenarbeit auf dem zweiten internationalen pädiatrischen Kongress in Stockholm 1930 zusammentreffen konnten. Der Kongress wurde ein Erfolg. Es muss gewiss einer der stolzesten Augenblicke im Leben JUNDELLS gewesen sein, an der Spitze dieses geglückten Zusammentreffens stehen zu können. Er hatte diesen Triumph ehrlich verdient. Sein Name, der schon vorher in den internationalen Kreisen nicht unbekannt war, zog durch diesen Erfolg noch mehr Aufmerksamkeit auf sich, und er nahm an den folgenden internationalen Kongressen als Teilnehmer einen selbstverständlichen Platz unter den zentralen Gestalten ein.

Nicht selten wehten harte Winde um ISAK JUNDELL. Er wurde wie so viele andere Bahnbrechernaturen oft ein Mann des Streites. Und doch liebte er Streit nicht. Seiner Natur nach war JUNDELL ein freundlicher und gutmütiger Mann, anspruchslos und bescheiden. Er gehörte zu den Menschen, für die das Wort Ruhe kaum existierte. Er war eine wirkliche Arbeitsnatur, vom Morgen bis zum Abend tätig. Ein Hobby in des Wortes eigentlicher Bedeutung hatte er nicht. Die Pädiatrik war und blieb sein beständiges Interesse, auch nachdem das Emeritusalter seine Laufbahn als aktiver akademischer Lehrer beendet hatte.

Im letzten halben Jahr wurde JUNDELL von dem Leiden, Kardiosklerose beschwert, das sein Leben beenden sollte. Verschwiegen, wie er in gewissem Masse über sich selbst war, behielt er auch dieses meist für sich. Wenige seiner Freunde ahnten, ehe die schwere, unheilbare Attacke einige Wochen vor seinem Tode kam, was er hieran trug. Bis zu den letzten Tagen kreisten seine Gedanken gern um die »Acta« und den nahenden nordischen pädiatrischen Kongress in Finnland. Aber es sollte ihm nicht mehr vergönnt sein, weiter mit uns zu wandern.

Nun ist ISAK JUNDELL nicht mehr. In Stille, so wie er es selbst gewünscht hatte, und wie es so gut zu seinem ganzen Leben passte, wurde sein Sarg unter Anwesenheit der Angehörigen, seiner nächsten Freunde, Schüler und Mitarbeiter in die Erde gesenkt. Sein Körper gehört dem Vergänglichen. Aber das Andenken an den erfolgreichen Forscher, Neugestalter und den guten Menschen wird in vielen dankbaren Herzen in und ausserhalb der Grenzen unseres Landes weiterleben.

Requiescat in pace!

Wilh. Wernstedt.

FROM THE 'EMMA' HOSPITAL FOR SICK CHILDREN, AMSTERDAM.
CHIEF PHYSICIAN: PROF. DR. CORNELIA DE LANGE.

Parapneumonic bullous emphysema in infants.

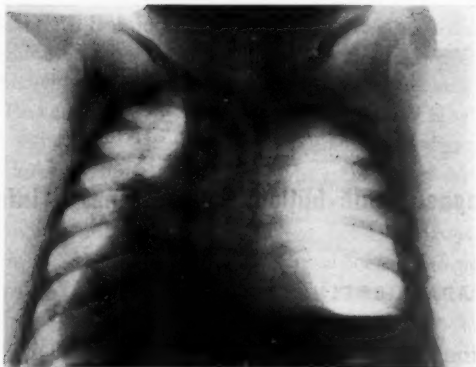
By

Dr. **ADA MIDDELHOVEN**, clinical assistant at that time.

In August 1944 a pretty, half-cast negro boy, aged six months, is admitted to the children's Hospital. Two days before he had fallen acutely ill, with cough and dyspnoe, after some slight symptoms of an infection of the upper respiratory tract a few days before. The further history of the patient and his family is irrelevant.

On examination the child appears to be well built and well nourished; he is acutely ill and dyspnoic. He always turns over on his right side, when lying in his cot, with his head thrown backside and the thorax protruding; the nostrils move in respiration. Temperature is 104°. In the lungs resonance is impaired in the upper part of the right side of the thorax; here breath sounds are weaker than elsewhere. The heart appears normal on percussion and auscultation, and further examination reveals no abnormalities.

Two days later impairment of resonance is noted over the lower part of the right lung, with fine moist rales. The child is dyspnoic, but otherwise only moderately ill. During the following days the dullness becomes more pronounced, while breath sounds are quite weak over the entire right half of the thorax; laterally on the right there are resonant rales; the heart is not displaced. The child growing calmer, with fever still remaining high, resonance on the tenth day appears to be much more sonorous; consequently but little dullness is left. Breath sounds, however, are still very weak, and so is the bronchophonia over the right lung; in the lower lateral part on the right some moist rales and a pleural rub are heard. Fever does not abate on chemotherapy. The physical signs indicate a pneumothorax, while fever and dyspnoe still suggest pneumonia. A roentgenogram, taken to elucidate these observations (photo 1.), yielded a great surprise. While the left lung appears to be normal, the right side of the thorax proves to be occupied by a large, air-containing cavity. There is some difficulty in determining the boundaries of the cavity; nowhere does it reach the thoracic wall. Part



1. Large cavity with air-fluid level, occupying the entire right half of the thorax and protruding into the left half. Lung tissue visible between the bulla on one side and the thoracic wall and the diaphragm on the other side. The organs of the mediastinum anterius are not displaced.

of the lung is visible at the apex, laterally, and over the diaphragm, without there being consolidation in those regions. On the medial side the situation is still more complicated: near the vertebral column some lung tissue is visible, but this does not appear to be a collapsed lung; the cavity reaches far into the left part of the thorax. Heart, trachea and bifurcation are but slightly out of place and therefore it must be the posterior mediastinum, that is displaced by the cavity. The cavity is marked by a finely traced borderline and contains a distinct air-fluid level, the mobility of which is demonstrated on roentgenograms with the child in a reclining position. A diagnosis of this finding as a partial pneumothorax cannot be upheld, it being hardly possible that in an infant pleural adhesions at the apex and in the sinus phrenicocostalis could be so strong, as to resist the air pressure in this distended cavity. Therefore one must conclude, that the cavity is situated intrapulmonally and extrapleurally, which in the literature on this subject is known as bullous emphysema.

This phenomenon has first been described by LAURELL (1), who emphasises its importance in the interpretation of the so called ring shadows in the roentgenograms in pulmonary tuberculosis. He also saw these cavities, surrounded by infiltrated lung tissue, in infantile pneumonia. Air-containing cavities in

pneumonic lungs have been frequently mentioned in the literature of later years. DUKEN (2) describes them in an infant aged four months, under the name of 'pneumatocele', and he quotes a post mortem report of BURGHARD (23) on an analogous finding. VOLLMER (3) gives a description of a pneumatocele in an infant aged ten months, which closely resembles our case history, with the exception of the air-fluid level. KLEINSCHMIDT (4) calls these cavities 'pseudocaverns', and observes them in pneumonia with *resolutio retardata*; his roentgenograms of benign abscesses of the lung following pneumonia cannot be distinguished from these emphysematous bullae with air-fluid levels. ZARFL (5) observes in a child aged seven months, suffering from recidivating pneumonia, the appearance, with marked dyspnoe, of an air-containing cavity under high pressure, the heart and mediastinum being displaced. Four months later all symptoms had disappeared. He, too, terms it a 'pneumatocele', »geschwulstförmige Luftansammlung«. His roentgenograms closely resemble ours, with the only difference that in his case the bulla was situated in the mediastinum anterius and did not contain any fluid. LEREBoullet et al. (6) describe a, probably parapneumonic, air-containing cavity in the lower part of the lung, disappearing in two months. MATHEJA (7) observes these transient cavities as complications of pneumonia, in two infants. In the past few years BENJAMIN & CHILDE (8) and CAFFEY (9) demonstrate longer series of patients, nineteen and twenty typical cases respectively, with rapidly disappearing cavities in pneumonic lungs, some containing fluid. In Holland the phenomenon has been seen in infants by E. A. TILLEMA (10) and by E. MEERMAN-SCHRÖDER (11); the latter describes a child, aged six months, admitted in our hospital for pneumonia, of whom the roentgenograms on the tenth day show a cavity with air-fluid level, disappearing in one month.

Among the case histories published with diagnoses of all kinds of pulmonary conditions, a goodly number are found, that in our opinion might be diagnosed retrospectively as pulmonary bullous emphysema. SCHENCK (12) sees an air-containing cavity in an infant, diagnosed by him as congenital cystic disease of the lung, disappearing completely after three months, which

renders his diagnosis speculative. KESSEL (13) observes quickly regressing cavities as complications of pneumonia, in five adults, some of which present an air-fluid level; he gives a diagnosis of a putrid necrosis of the lung, and quotes some post mortem findings of this condition. Of the latter he gives neither clinical nor roentgenological data so that it is impossible to identify these post mortem findings and the transient cavities in his clinical histories; his roentgenograms resemble closely those of CAFFEY. LAURELL (1) distinguishes two modifications of bullous emphysema. In the first one air is pressed in the interstitium of the lung, which fact he demonstrated by inflation of the lungs of a calf; the second consists of a great number of distended alveoli, with destruction of the interalveolar walls; sometimes there is also general emphysema. MILLER (14, 15, 16) gives remarkable anatomical descriptions, both macroscopic and microscopic. The general opinion is that these cavities originate by a check-valve mechanism. Thickening of the mucous membranes, plugs of secretion or scar formation cause a partial obstruction of the afferent bronchioli; this obstruction is shown anatomically by MILLER (16), FISHER—WASELS (17), and HAYASHI (18); the check valve mechanism is accentuated by the fact that the bronchioli become wider and shorter in inspiration, and longer and narrower in expiration (LAURELL (19), SPIVEK (20)). In the normal lung this mechanism is counterbalanced by the interalveolar pores of KOHN; these are obliterated by pneumonic consolidation, and thus the bullae grow more and more distended (CAFFEY (9)).

That these conditions are observed almost exclusively in infants is argued by the fact, that the lung tissue at this age is fragile and contains but few elastic fibres (FREEDMAN (21), MATHEJA (7); persistent and violent coughing suffices to cause a rupture of the alveolar walls (ARNELL (12)). ZARFL (5) offers a different hypothesis; he assumes the infiltrated lung to be destroyed first, this destruction leading to a pulmonary abscess, the pus being expectorated and the resulting cavity inflated with air by check-valve mechanism.

In order to preclude other possibilities of accumulation of

air in the thorax artificial pneumothorax, bronchographical application of iodized poppyseed oil and puncture might be resorted to. Artificial pneumothorax is advocated by KLEIN-SCHMIDT (7); he apparently did not apply it himself. The Americans on the contrary opine this measure contraindicated and indeed unnecessary if a careful X ray examination is made. Only one case of artificial pneumothorax is mentioned, by MATHEJA, caused accidentally by puncture of the cavity, a roentgenogram showing the large bulla as an appendix to the completely collapsed lung. Bronchography, too, is rejected as a diagnostic measure by BENJAMIN & CHILDE (8). There are no applications of this diagnostic mentioned in the literature.

If these cavities are punctured a high intracavitary pressure is always found (DUKEN (2), MATHEJA (7)). In both their cases the cavity rapidly disappears after this intervention (post aut propter). But in all the cases mentioned, the benign and transitory character of the condition is striking, even in cases of air-fluid levels. The cavity generally disappears soon before or after the resolution of the pneumonic consolidation.

The character of the fluid contained in the cavity, is but seldom mentioned. In SCHENK's (12) case a brownish fluid was expectorated from the cavity; at the post mortem of BURG-HARD's (23) a small quantity of pus is found, containing staphylococci.

We, too, endeavoured to puncture the cavity in our patient. A small quantity of pus with air is evacuated, the pus containing staphylococci. In the two weeks following the puncture the general condition is stationary; breathing becomes amphoric in the right interscapular region; on roentgenograms (photo 2.) the cavity appears slightly reduced in size; the displacement of the mediastinum posterius is less marked and a greater part of expanded lung tissue is visible over the diaphragm; at the apex, however, consolidation remains. The temperature, however, that had dropped to normal, rises again to about 100°.4. The general condition gets worse. The child becomes emaciated and listless and appetite is lost; he appears to be chronically ill. Realising the failure of conservative therapy, surgical intervention is called in in order to drain the cavity. A thoracotomy (Dr. Harrenstein) is performed on the right laterally and about a hundred cc. off pus is discharged under high



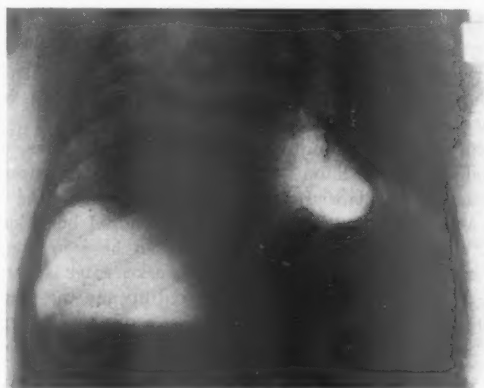
2. The bulla has diminished in size; consolidation of the left lung at the apex.



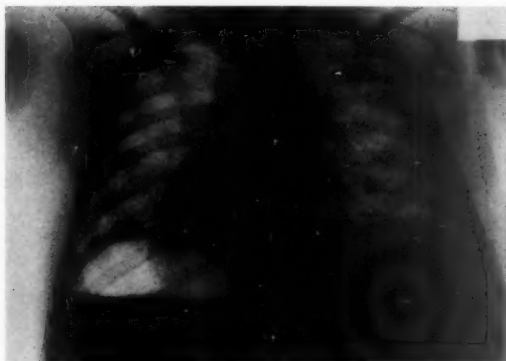
3. Immediately post operationem. Cavity partly collapsed. Second bulla visible.



4. Original bulla has disappeared. Expansion of the second one, equally protruding into the left part of the thorax.



5. The drain has been removed. Further expansion of the second bulla.



6. There is no trace left of both cavities at the time of discharge from the hospital.

pressure. The temperature after the operation immediately drops to normal and the general condition is very much improved; the child begins to play, regains his appetite and in the two weeks following the operation gains 600 grams in weight.

Roentgenograms immediately following the operation (photo 3.) show the cavity free from fluid and partly collapsed; after four days the cavity has roentgenologically disappeared. This roentgenogram (photo 4.), however, discloses the presence of a second bulla, situated distally and medially to the original cavity and also protruding into the left part of the thorax; it contains no fluid. A physical examination reveals hyperresonance on both sides of the spine. The general condition is not influenced by the presence of this new bulla.

On a renewed examination of the other roentgenograms, we find the new bulla already immediately after the operation; apparently it was already present in a collapsed state and now expanded by the check valve mechanism after the counterpressure of the original bulla subsided. In a series of roentgenograms this new bulla can be seen diminishing in size, with complete disappearance four weeks after its appearance. Another week later the right lung has cleared up and the roentgenogram has become normal again (photo 6.) The child has grown a sturdy little fellow and has gained three pounds in weight since the operation.

This case history demonstrates, that parapneumonic bullous emphysema when not complicated, is a fairly innocent condition, showing merely symptoms of compression; therapeutical measures

are not required. Secondary infection of the fluid in the cavity resulting in an empyema, may cause a condition, which seriously affects the general health and we consider the operation to have been a life saving procedure in our case.

December 1944.

Summary.

The author gives the case history of a six months old infant, suffering from bullous emphysema as a complication of pneumonia, with survey of the literature on this condition. The child is seriously ill from a staphylococcal empyema originated in the emphysematous bulla, and makes a recovery only after a thoracotomy has been performed. Postoperative expansion of a second bulla, which disappears without having given any symptoms. Complete recovery.

Résumé.

L'Auteur présente le cas d'un enfant, âgé de six mois, souffrant d'un emphysème à grosse bulle solitaire, complication d'une pneumonie. Exposé de la littérature sur ce sujet. L'Enfant est grièvement malade à cause d'une infection staphylococcique de l'épanchement dans la cavité bulleuse. Succès prompt et remarquable d'un drainage par thoracotomie. Dans la période postopératoire développement d'une seconde bulle non infectée, qui disparaît sans avoir causé de symptômes.

Zusammenfassung.

Es wird ein Fall von bullösem Emphysem beschrieben mit ausserordentlich grosser Blase im Verlaufe einer Pneumonie, bei einem sechs Monate alten Säugling. Schwere Beeinträchtigung des Allgemeinzustandes durch Staphylokokkeninfektion des Exsudats in der Emphysemlase. Prompte Besserung nach operativer Drainage. Entfaltung einer zweiten, nicht infizierten Blase, die symptomlos wieder verschwindet. Restitutio ad integrum. Literaturübersicht.

References.

1. HUGO LAURELL: *Acta radiologica* 4, 634—, 1925. — 2. J. DUKEN: *Zeitschrift für Kinderheilkunde* 43, 339—, 1927. — 3. H. VOLLMER: *Zeitschrift für Kinderheilkunde* 46, 810—, 1928. — 4. H. KLEINSCHMIDT: *Monatsschrift für Kinderheilkunde* 46, 205—, 1930. — 5. M. ZARFL: *Zeitschrift für Kinderheilkunde* 54, 92—, 1933. — 6. P. LEREBOULET, M. LELONG, & J. BERNARD: *Bull. soc. med. hôp. Paris*, 53, 506—, 1937 (reference). — 7. W. MATHEJA: *Zeitschrift für Kinderheilkunde* 60, 236—, 1938. — 8. B. BENJAMIN & CHILDE: *J. of Pediatrics* 15, 621—, 1939. — 9. J. CAFFEY: *Amer. J. dis. Childr.* 60, 586—, 1940. — 10. E. A. Tillema: *Ned. Tijdschr. v. Geneesk.* 84, 3666—, 1940 III. — 11. E. MEERMAN-SCHRÖDER: *Maand-schr. v. Kindergen.* 12, 322—, 1943. — 12. S. G. SCHENCK: *Amer. J. Roentgen.* 35, 604—, 1936. — 13. L. KESSEL: *Arch. intern. Med.* 45, 401—, 1930. — 14. W. S. MILLER: *Amer. J. Roentgen.* 15, 399—, 1926. — 15. —: *Amer. J. Roentgen.* 18, 42—, 1927. — 16. —: *Amer. Rev. of Tuberc.* 28, 359—, 1933. — 17. FISCHER-WASELS: cited by FREEDMAN. — 18. HAYASHI: cited by FREEDMAN. — 19. HUGO LAURELL: *Acta radiol.* 10, 72—, 1929. — 20. M. L. SPIVEK: *Amer. J. dis. Childr.* 51, 69—, 1936. — 21. E. FREEDMAN: *Amer. J. Roentgen.* 35, 324—, 1936. — 22. S. ARNELL: *Acta Radiologica* 8, 252—, 1927. — 23. BURGHARD: *Fortschr. a. d. Geb. d. Roentgenstr.* 34, 308—, 1926.

FROM THE QUEEN LOUISE HOSPITAL FOR CHILDREN, COPENHAGEN.
CHIEF: PROFESSOR OLUF ANDERSEN, M. D.

Hæmangio-endothelioma of the Liver.

By

AAGE VIDEBÆK.

Angio-endothelioma of the liver is a very uncommon disease, the literature containing reports of only about 30 cases, nearly half of which are children. Since the disease has not been dealt with earlier in Scandinavian literature, the writer below gives a brief description of its pathology, pathogenesis, and clinical features on the basis of a review of all earlier cases and one case of his own.

After an oral statement in 1908 FISCHER in 1913 gave a detailed description of a tumour of the liver occurring in a man, aged 45. The liver was greatly enlarged, containing numerous dark red, indistinctly demarcated nodules which on microscopic examination proved to consist of blood-filled spaces, divided by an extremely proliferative endothelium, in places transformed into myelopoietic tissue. A diagnosis of multiple malignant hæmangio-endothelioma was passed. Ever since, this description has served as the classic model of similar cases, although the total number of hæmangio-endotheliomas reported to have been found in the liver is very low. As early as 1885, however, CHERVINSKY published a case occurring in a boy, 6 months of age, who exhibited several hepatic growths of varying size which according to his description no doubt must be interpreted as an angio-endothelioma, although no mention is made of hæmopoietic function on the part of the endothelial cells. DE HAAN (1903) also found numerous, cystic hæmangio-endotheliomas in the liver of a baby, aged 1 month. LÖHLEIN (1909) reported a case occurring in a 32-year-old man. The case reported by WEEDER &

AUSTIN (1912), a baby girl of $2\frac{1}{2}$ months, exhibited numerous hepatic nodules, very reminiscent of simple hæmangiomas, but there was a definite proliferation of endothelial cells. Unlike the above-mentioned cases the one described by KOTHNY (1912) consisted of one large tumour in the cirrhotic liver of a patient, aged 54. HACHFELD (1914) was the first to report metastases (lymph nodes in the porta hepatis and the lungs) from the numerous endotheliomas of the left hepatic lobe of a woman, aged 43, who also displayed some cirrhosis. The case reported by KAHLE (1919), a 58-year-old man, bears a close resemblance to FISCHER's case, whereas FOOTE (1919) was unable to demonstrate hæmopoietic function in the tumour of a baby, aged 3 months. In the cirrhotic liver of a 57-year-old man SCHLESINGER (1920) found numerous nodules which turned out to be hæmangio-endotheliomas. GÖDEL has reported numerous hæmangio-endotheliomas of the liver occurring in 3 patients, a baby of 3 months (1923), a man, aged 69 (1923) with a co-existent, marked cirrhosis, and a woman, aged 72 (1930); in the case of the two last-mentioned patients the endothelial cells in places were found to produce erythroblasts as well as myeloid cells. In one case, a man aged 42, closely resembling the two last-mentioned ones, SCHÖNBERG (1923) found the blood to contain normoblasts, megaloblasts, and myelocytes. Another case (in a 23-year-old patient) reported by the same author differs from those mentioned above in exhibiting *only one* blood-forming hæmangio-endothelioma, measuring, however, no less than 10×7 cm in diameter. In the author's opinion it arose in a cavernoma. In addition to tumours of the liver a case reported by SMITH in 1926 displayed hæmangio-endotheliomas in the lymph nodes, spleen, adrenals, lungs, heart, and omentum, taken to represent metastases from the hepatic tumours. Unlike one of NEUBÜRGER & SINGER's 2 patients (1927) who corresponded to FISCHER's description, the case reported by BLUMBERG (1926) failed to display blood formation. ORZECOWSKI (1928) observed numerous hæmangio-endotheliomas in the liver of a baby, aged $2\frac{1}{2}$ months, with metastases to the skin and lungs, and DASSEL (1928), reporting a similar case in a 56-year-old woman found metastases from the liver to the spleen, one lung, the iliopsoas

muscle, spinal column, ribs, and to the skull. SPIEGEL in 1929 described a globular, pedunculated hæmangio-endothelioma, 15 cm in diameter, arising in the right hepatic lobe of a 13-month-old baby. Presumably this case (like the majority of those mentioned above) had a number of other tumours in the liver, which was described as exhibiting several grey-brown patches. GOODALE (1930) found several hæmangio-endotheliomas in a baby, 11 months of age. PUHR (1931) found metastases in the pancreas of a 56-year-old man. WHITE (1933) described a typical, extremely polymorphous hæmangio-endothelioma containing a number of giant cells as well as mitoses and metastasizing to the lungs, pancreas, and retroperitoneal lymph nodes. KUNSTADTER's patient was a baby-girl, aged 5 months. GESCHICKTER & KEASBEY (1935) briefly mention 3 patients, aged 9 months, 2 years, and 2½ years, who exhibited multiple, malignant endothelio-blastomas in the liver. In HOWARD's case (1936), a 3-month-old baby, the hepatic tumour co-existed with a small hæmangioma of the colon and one of the skin. KARDJIEV's patient (1938), a 27-year-old woman, exhibited a liver containing numerous hæmangio-endotheliomas with myelopoiesis and erythropoiesis as well as metastases in the portal lymph nodes and one lung. The growths were cystic. The most recent case was reported by BENDICK in 1939. The patient was a man, aged 57, who also exhibited a similar tumour in one lung.

Below the writer reports an additional case of hæmangio-endothelioma of the liver observed at the Queen Louise Hospital for Children, Copenhagen:

♂, F. B., case rec. No. 741/44. Only child of sound parents, born at full term and breast-fed. Hospitalized at the age of 2½ months on account of constipation, pallor, and general weakness. Length 55 cm, weight 4550 kg. The baby was pale and rather thin, but had an enlarged abdomen. The left external ear and the skin covering the tuberosity of the tibia were the sites of a superficial, cavernous hæmangioma, measuring about 2 × 3 mm. A number of lymph nodes, as large as rice seeds, were observed on both sides of the neck, in both axillæ and inguinal regions. Along the left border of the sternum there was a somewhat rough, systolic murmur. Electrocardiogram and roentgenograms of the heart and lungs revealed normal conditions. The skin of the

distended abdomen was taut. There was an umbilical hernia, as large as a hazel nut, and a left-sided inguinal hernia, as large as a walnut. Increased venous pattern on the abdomen. On palpation the liver was enlarged, rather firm, apparently with a smooth surface and a somewhat blunt inferior margin, extending to a site 4—5 fingerbreadths below the costal border, passing the navel, and losing itself below the left costal border. The lower splenic pole was about 2 fingerbreadths below the costal border. The clinical examination did not reveal ascites. The anal sphincter was tight and the ampulla contained dry faecal matter.

The baby gradually lost ground, it was quiet and still, unwilling to drink, vomited a good deal, and did not thrive. The temperature was subnormal, and the anaemia remained marked in spite of repeated blood transfusions. Following an even downhill course, the baby died at the age of 4 months.

Hæmoglobin percentage was about 60, colour index about 1. Mean diameter of erythrocytes 6.6μ . Icteric index 13. The fragility of the red cells was normal. Micro-sedimentation rate 5—7 mm. Wassermann test negative. Tuberculin reaction negative. Leucocytes 4 000—8 000. Differential count revealed 1 to 2 per cent erythroblasts, about 1 per cent myelocytes. Thrombocyte count 280 000. Prothrombin time 115—96, bleeding time $4\frac{1}{2}$ minutes. Bone marrow (tibia): Normoblastic, definitely a somewhat reduced erythropoiesis, normal myelopoiesis. Serum protein 5.2 per cent, serum albumin 4.3 per cent, serum globulin 0.9 per cent.

The stools were not acholic, and of the aspect normally encountered in breast-fed infants. The urine contained no albumin, sugar, urobilin, bile pigments, aceto-acetic acid, or acetone. Microscopic examination of the urine revealed nothing abnormal.

Takata Ara test normal. Fasting blood sugar 72—79 mg per cent, tolerance test with 1.75 g glucose per kilo body weight was followed by a rise in the blood sugar value to a maximum of 190 mg per cent in the course of half an hour. $2\frac{1}{2}$ hours after the administration the values had returned to normal. 1 hour after the subcutaneous injection of $\frac{1}{4}$ mg adrenaline the blood sugar reached its maximum value of 80 mg per cent. The highest blood sugar value obtained by the subcutaneous administration of $\frac{1}{2}$ mg adrenaline was 115 mg per cent, also one hour after the injection.

Repeated roentgenograms of the abdomen revealed an increasing shadow at the site of the liver and of the same shape, reaching at last to the right crest of the ilium. Besides, there was an appreciable soft mass in the splenic region. Roentgen examination of the entire skeletal system revealed normal conditions.

Accordingly, the likelihood of hepatic cirrhosis and a primary or secondary tumour of the liver had to be seriously contemplated. An

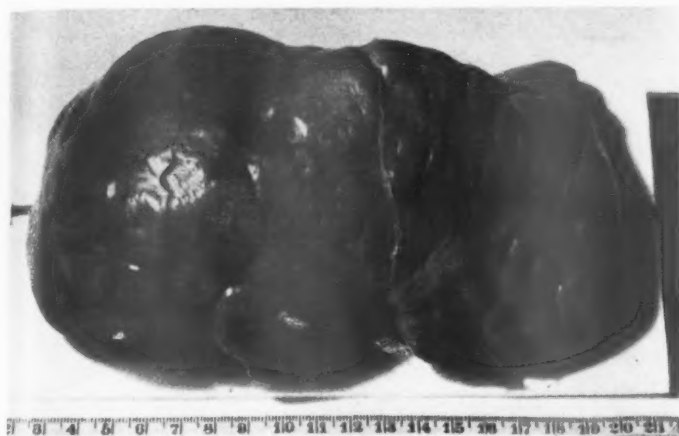


Fig. 1. Greatly enlarged liver with numerous, grey white, umbilicate haemangio-endotheliomas.

aspiration biopsy from the liver was now performed (K. ROHOLM). Microscopic examination of the specimen (Sv. PETRI) revealed: The hepatic tissue is of a uniform structure, with normal staining quality. The cells are mostly of medium size, more rarely somewhat smaller, in a few cases containing fat. The glycogen content is presumably somewhat less than normal. Slight, chronic inflammatory changes in the periportal area.

Autopsy: Some ascites. The greatly enlarged liver, measuring $18 \times 10 \times 6$ cm, is the site of numerous, extensive nodules, ranging in size from a few mm to 3–4 cm in diameter, with even intervals. On the surface of the liver (Fig. 1) the nodules appear in the form of grey-white, umbonate structures, now distinctly, now indistinctly demarcated from the hepatic tissue. On cut section (Fig. 2) the centre of the nodules is bluish red and the peripheral area somewhat lighter than the remaining, normal hepatic tissue. In some of the nodules this difference is not particularly marked and the pattern reminds of mosaic. The nodules are so densely placed that it is surprising that the hepatic function was not further compromised and that the biopsy specimen did not contain neoplastic tissue. The gross appearance of the nodules, the umbonate shape, and the reddish central area, suggest typical carcinoma metastases, but tumours which might have caused the presumed hepatic metastases are not demonstrable in the stomach, intestinal canal, pancreas, biliary ducts, lungs, adrenals, kidneys, or testes.



Fig. 2. Numerous, bluish red hæmangio-endotheliomas of unequal size in the liver.

Microscopic Examination (O. WANSCHER): The tumours present in the liver are of a rather uniform structure and for a large part consist of a huge number of fairly densely placed, more or less blood-filled locules of an irregular shape and lined with endothelium, in places suggesting a cavernoma and in other places hæmangioma. The stroma forming the ground substance of the vascular elements consists of a dense, moderately cellular, collagenic connective tissue without inflammatory processes, present or past hæmorrhage, or necrosis. No fresh or past thrombosis. No signs of hæmatopoiesis. There is some proliferation of endothelial cells, particularly in the peripheral area of the neoplastic tissue, which area is of a more solid construction, less like a cavernoma. The stroma at this site presumably also is richer in cells which in places almost remind of reticulo-endothelial tissue. The neoplastic tissue is traversed by major branches of vessels of arterial as well as venous character. Besides, one frequently comes across the split fragments of normal biliary passages and small rows of hepatic cells. The surface of the tumour is somewhat irregular and indistinctly delimited, it seems to invade the hepatic tissue, resulting in a splitting and pressure atrophy of the latter. There is no connective-tissue capsule. The hypertrophic and hyperplastic endothelial cells (respectively stroma cells) only exhibit extremely few bipolar mitoses, but, on the other hand, there were no atypical mitotic figures, no cells with large or multiple

nuclei, no major tenon or islet-shaped proliferation of the cells as seen in typical, malignant processes.

The hepatic tissue in between the tumours is of a uniform, normal, lobular structure without atrophy of the hepatic cells, accumulation of fat, or pigmentation. Doubtful hyperæmia (stasis) and a doubtful, diffuse increase of the connective tissue. The periportal spaces are not enlarged, but in places infiltrated by round cells. The biliary ducts are natural.

When regard is paid to their construction and character on the whole the tumours presumably are: *Primary, multiple hæmangio-endotheliomas of the liver.*

Discussion.

Thus we have an additional case of hæmangio-endothelioma of the liver, occurring in a boy, aged $2\frac{1}{2}$ months, dying at the age of 4 months. Death, no doubt, was due to inanition, the liver occupying so large a part of the abdomen, that the food constantly was rejected. The examinations *in vivo* mentioned above ruled out the diagnoses of hepatic cirrhosis, hæmolytic jaundice, leukæmia, anæmia infantum pseudoleukæmica, and Gierke's disease. Stasis of the liver was out of the question in view of the slight symptoms of cardiac insufficiency. There was a considerable probability of hepatic neoplasm which, judging by its rapid growth, must be considered as malignant. It is true that a tumour of the liver seldom is encountered during childhood, but of course it does occur in rare cases, especially in the form of the primary, malignant hepatic tumour. Even in adults primary cancer of the liver is uncommon. Reviewing the literature up to 1930 HERXHEIMER only found 439 cases of primary carcinoma of the liver. 10 per cent of the cases had occurred among children below 10 years of age, and 27 patients were between 10 and 20. Among 16 565 patients passing through The Memorial Hospital during the period 1917—1929 PACK & LEFÈVRE found only 28 suffering from primary carcinoma of the liver, the youngest patient being 22 years of age. Revising the diagnosis of primary hepatic carcinoma in childhood STEINER in 1938 only could accept the diagnosis as correct in 75 out of 105 published cases. 53 per cent of the children had acquired the disease before 2 years of age.

Primary sarcoma of the liver is still more uncommon than

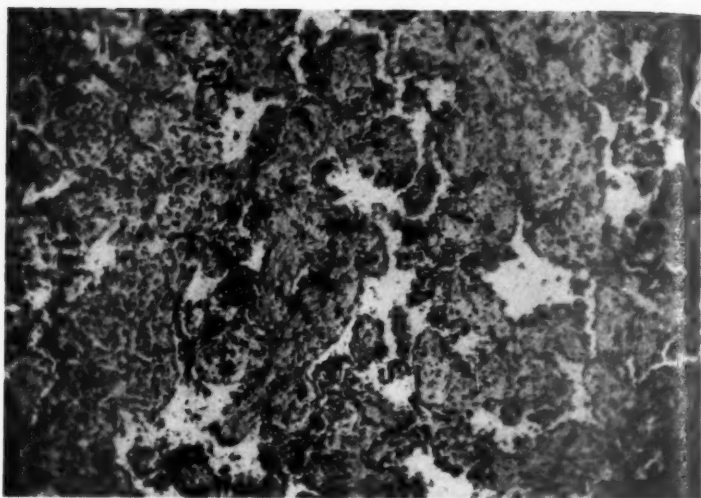


Fig. 3. Irregular, blood-filled spaces, lined with endothelial cells, from the central part of the tumour (105 \times).

primary hepatic carcinoma, but still, the 66 cases of hepatic sarcoma dealt with in HERXHEIMER's publication included no less than 23 per cent in the age group 0—10 (against 10 per cent of the carcinomas). This observation is in accordance with the general rule that sarcomas are comparatively frequent in childhood.

It is of course difficult to decide whether a tumour of the liver is primary or secondary, the source of the tumour, if secondary, often remaining occult for a long time. In the case of our patient there was nothing to indicate a tumour in the alimentary canal, the pancreas, kidneys, or adrenal glands. The only findings which might have drawn attention towards the diagnosis: vascular new growth in the liver, were the 2 cutaneous hæmangiomas. Skin hæmangiomas, on the other hand, frequently are encountered as isolated phenomena. It should be kept in mind, however, that hæmangiomas often are multiple and sometimes metastasize (BRÜCHANOW 1899, GESCHICKTER & KEASBEY 1935, WOLLSTEIN 1931), and ORZECZOWSKI (1928) and HOWARD

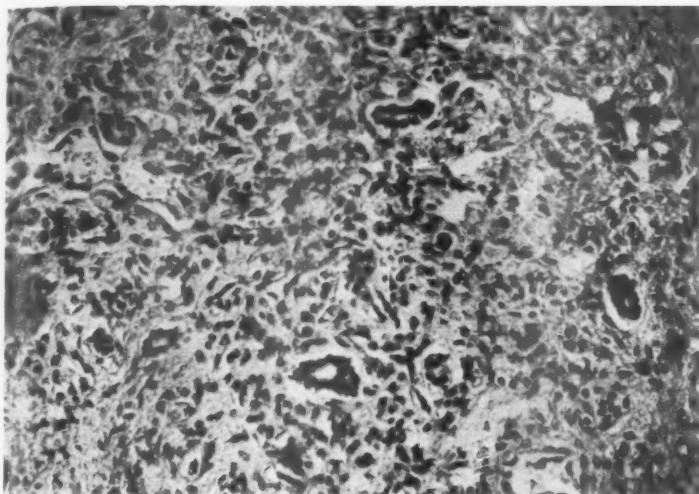


Fig. 4. The peripheral area of the growth is massive. The cells are uniform, rather highly differentiated. Spread biliary passages with a well-preserved structure (225 \times).

(1936) both observed skin haemangiomas co-existent with haemangio-endotheliomas of the liver. The diffuse occurrence of this kind of tumour in the liver is to be interpreted as a multicentric development of new growths and not as metastases. Histogenetically it is probably a question of a defect in the endothelium of the hepatic capillaries which have retained an embryonal character, resulting in a proliferation of endothelial cells, the formation of young fibrillar connective tissue, and (like other cases) the formation of erythroblasts and cells of the myeloid system. Maybe the tumour originated in Klupffer's cells which in several places exhibited a swollen, hyperchromatic nucleus. In the present case too, the tumour must be considered as histologically benign, arising multicentrically on account of an endothelial defect.

In the microscopic preparation the central area of the individual tumours was characterized by numerous, blood-filled

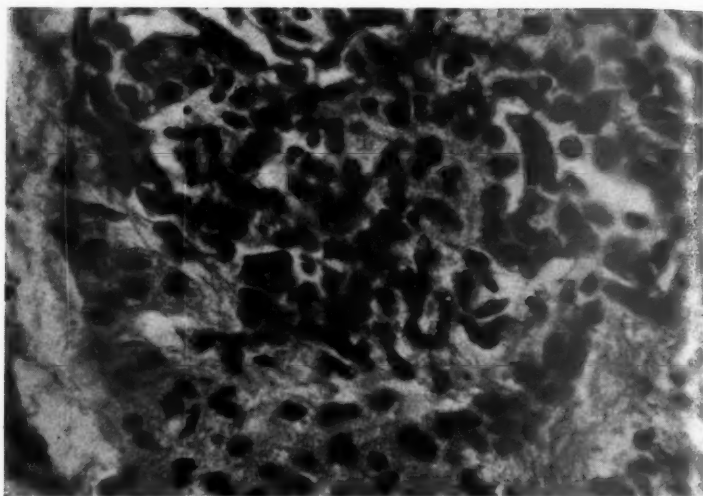


Fig. 5. Islet of proliferative endothelial cells splitting the hepatic cells (580 \times).

spaces with an endothelial lining (Fig. 3). The peripheral parts on the whole were of a more massive construction, conveying an impression of uniform architecture with rather highly differentiated cells, respecting the spread biliary passages (Fig. 4). Fig. 5 shows proliferation of endothelial cells between detached islets of hepatic cells. There was no cirrhosis of the liver. None of the sections examined revealed erythroblasts or myeloid cells. The fact that these forms of cells still were demonstrable, though in slight quantities, in the circulating blood, may be due to a differentiation of the endothelial cells constituting some of the numerous, non-examined nodules, so extensive as to form the source of the immature blood corpuscles which, however, may have been of some other origin.

Reviewing the cases of hæmangio-endothelioma of the liver reported in the literature accessible at the moment, the writer has omitted the cases which are not interpretable as actual endotheliomas. The cases thus collected are 32, and adding the case

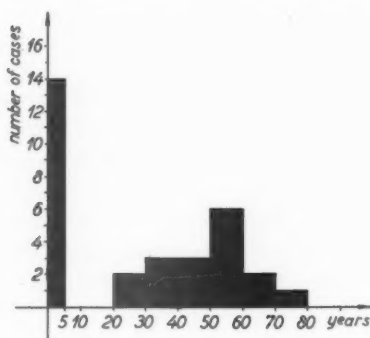


Fig. 6. Age chart presenting 31 patients suffering from hæmangio-endothelioma of the liver.

reported by the writer the total number of patients amounts to 33. 13 were males and 11 females, in 9 cases the sex was not given. The mean age was about 25 years. 14 of the patients were children, the eldest being $2\frac{1}{2}$ years and the youngest 1 month of age. The mean age in the case of the children was 8 months. The mean age among the adults was about 49 years (eldest 72 years and youngest 23). The diagram, giving the age distribution, has two summits, one during infancy, and the other in the 5th decennium, whereas the age period 3 to 20 is tumour-free. The patients in the 5th decennium exhibit an age distribution similar to patients affected with, e.g. mammary gland cancer. In some way or other there seems to be a fundamental difference between the growths observed among infants and those occurring in adult patients. Apart from the somewhat more rapid course of the disease which seems to be a peculiarity of neoplastic disease in childhood, the clinical features of both groups hardly differ. The two groups do not either seem to display any histological difference in the construction of the tumour, but, unlike children, adult patients frequently exhibit cirrhosis of the liver. The histological construction of the tumours being exactly the same in both groups, there is no reason to presuppose a difference in the pathogenesis of the growth occurring during infancy and the one acquired in adult life.

In both cases, no doubt, it is a question of a defective development of the vascular system of the liver, originating in the embryonal tissue. As far as the infant patients are concerned, the tumour without a doubt is congenital. In adults the tendency to the growth, no doubt, has been latent from embryonal life, and presumably a factor, contingent on the age of the individual, has released the development of the tumour in the adult organism. Cirrhosis of the liver seems to be of some significance in this connexion as in the development of primary carcinoma of the liver.

The characteristic feature of the disease is the presence of numerous tumours, evenly distributed and spread almost diffusely over the entire liver. SCHÖNBERG has, however, reported a solitary hepatic tumour, 10×7 cm, presumably arising in a cavernoma and thus possessing a special pathogenesis. SPIEGEL has described a pedunculated tumour, measuring no less than 15 cm in diameter, co-existing, however, with diffuse changes of the entire liver, not submitted to microscopic examination. As a rule the hepatic growth has been marked. In GÖDEL's case (1930) the liver weighed 8 kg, and GOODALE (1930) found a liver weighing 1100 g in an infant, aged 11 months. The growths are generally described as bluish red, vascular tumours, bleeding on section, and very seldom (DE HAAN, KARDJIEV) cystic. DASSEL (1928) and GÖDEL (1930) have each reported a case of hæmangio-endothelioma, rupturing on the surface of the liver and resulting in a considerable peritoneal hæmorrhage and death. When keeping in mind the vascularity of the tumour, it is evident that aspiration biopsy of the liver is a dangerous intervention in the presence of hæmangio-endothelioma.

The tumour has been described as a histologically malignant growth (i. a. by FISCHER, KAHLE, SCHLESINGER, MILLER) presenting a rather motley picture with polymorphous cells, a few giant nuclei, numerous mitoses, and distinct vascular invasion. In such cases nodules of a similar construction occurring in other organs without a doubt may be taken to be metastases from the hepatic growths. In a few cases (e. g. HOWARD) the microscopic construction of the tumour does not reveal signs of malignancy, and extra-hepatic

nodules, if any, of a construction similar to the liver growth, therefore, should be regarded as primary, arising in the respective sites on account of the same endothelial defect that caused tumour formation in the liver. Apparently, the extra-hepatic tumours described in about one-third of the reported cases have no preferential localization. As a rule the tumours (the metastases) are situated in the lungs, where they may cause hæmoptysis, but they have been encountered in the spleen, pancreas, intestine, adrenals, omentum, heart, bones, muscles, and skin as well. As mentioned above the simultaneous occurrence of cutaneous hæmangioma and hæmangio-endothelioma of the liver has been observed in 4 cases.

In childhood as well as in adult life the disease is characterized by the enlargement of the liver, accompanied by a sensation, sometimes regular pain, in the right upper quadrant. In children the enlarged liver gives rise to frequent vomitings. Constipation also seems to be an outstanding symptom, be it due to inanition (pseudo-constipation) or the pressure of the liver on the colon. Emaciation and anæmia are natural consequences of this condition. Occasionally the blood has contained erythroblasts and immature myeloid cells, presumably originating in the hæmopoietic foci of the endothelium (SCHÖNBERG). Immature blood cells have been encountered in the blood, even in cases in which microscopic examination of the growth has failed to demonstrate hæmopoietic function which, however, may have been present in other tumours, not submitted to microscopic examination. Sometimes one may observe jaundice as well as ascites, now and then oedema of the lower limbs. The moderate enlargement of the spleen, which often attends the disease, is caused by stasis. As mentioned above, the occurrence of simple hæmangiomas in the skin may give a hint at the diagnosis, and the presence in other organs of growths of a construction similar to those appearing in the liver may constitute a conspicuous clinical feature (hæmorrhage).

The disease always runs a fatal course, either because the tumour is malignant and metastasizing or, if the tumour histologically is benign, because the growths are multicentric and gradually involve the entire liver, for which reason the clinical

aspect is one of malignancy. It is impossible to form an opinion of the duration of the disease. So far it has not been possible to apply any form of treatment.

Summary.

The writer briefly reviews the earlier reports of hæmangio-endotheliomas of the liver and adds a case of his own, occurring in a boy, aged $2\frac{1}{2}$ months, exhibiting numerous, histologically benign hæmangio-endotheliomas of the liver and 2 cutaneous hæmangiomas. A discussion follows of the pathogenesis of the disease in connexion with the demonstration of two summits in the age diagram, one in early childhood, and one in the 5th decennium. Finally, the pathological and clinical features are dealt with.

References.

- BENDICK, E.: Frankf. Ztschr. f. Path. 53: 234, 1939. — BLUMBERG, A.: Virch. Arch. 261: 82, 1926. — BONDY, J.: J. A. M. A. 56: 873, 1911. — BRÜCHANOW, N.: Ztschr. f. Heilk. 20: 131, 1899. — CHERVINSKY: Arch. de Physiolog. 6: 553, 1885. — DASSEL, A.: Frankf. Ztschr. f. Path. 36: 99, 1928. FISCHER, B.: Frankf. Ztschr. f. Path. 12: 399, 1913. — FOOTE, J.: J. A. M. A. 73: 1042, 1919. — GESCHICKTER, C. F. & KEASBEY, L. E.: Am. Journ. Cancer. 23: 568, 1935. — GOODALE, R. H.: Arch. Path. 9: 528, 1930. — GÖDEL: Zentralbltt. f. allg. Path. 48: 237, 1930. — GÖDEL, A.: Frankf. Ztschr. f. Path. 29: 388, 1923. — DE HAAN, J.: Beitr. d. Path. Anat. 34: 215, 1903. — HACHFELD, M.: Primärer Leberkrebs usw. Primäres malignes Endotheliom des Leber im Bilde einer Leberzirrhose. Thesis, Halle 1914. — HERXHEIMER, G.: Henke Lubarsch. 5/1, 1930. Springer, Berlin. — HOWARD, W. A.: Journ. Ped. 8: 588, 1936. — KAHLE: Über ein Hämogonien und Leukozytenerzeugendes Angiosarkom in zirrhotischer Leber. — Thesis, Jena. 1919. — KARDJIEV, B.: Frankf. Ztschr. f. Path. 51: 369, 1938. — KOTHNY, K.: Frankf. Ztschr. f. Path. 10: 20, 1912. — KUNSTADTER, R. H.: Am. J. Dis. Children. 46: 803, 1933. — LENDROP: Hospitalstidende 8: 217, 1893. — LÖHLEIN: Verhandl. d. deutsch. path. Gesellsch. 13th Meeting, 1909, p. 320. — MILLER, J. K.: Am. Journ. Surg. 44: 458, 1939. — NEUBÜRGER & SINGER: Frankf. Ztschr. f. Path. 35: 543, 1927. — ORZECOWSKI, G.: Virch. Arch. 267: 63, 1928. — PACK, G. T. & LEFEVRE, R. G.: Journ. of Cancer Research 14: 167, 1930. — PUHR, L.: Zeitschr. f. Krebsforsch. 34: 503, 1931. — SCHLESINGER: Primäres malignes Angioendotheliom in der zirrhotischen Leber. — Thesis,

Frankfurt 1920. — SCHÖNBERG, S.: *Frankf. Ztschr. f. Path.* 29: 77, 1923. — SMITH: *Arch. Path. and Lab. Med.* 1: 365, 1926. — SPIEGEL, H. A.: *Arch. Pediatr.* 46: 188, 1929. — STEINER, N. M.: *Am. Journ. Dis. Child.* 55: 807, 1938. — WEEDER, B. S. & AUSTIN, J. H.: *A. J. Med. Sci.* 143: 102, 1912. — WHITE, C. S.: *J. A. M. A.* 101: 119, 1933. — WOLLSTEIN, M.: *Arch. Path.* 12: 562, 1931.

Some Notes on the Mechanism of the so-called »Emotional Convulsions».

By

NILS LINDQUIST.

The so-called emotional convulsions are a well-known condition to every pediatrician. They are a reaction which we observe in infancy in the really temperamental child with labile affects and uninhibited emotional life, perhaps especially when there are good prototypes in his close surroundings. The credit of differentiating these attacks from laryngospasms on tetanoid basis is due to H. NEUMANN, while the term respiratory emotional convulsions was coined by IBRAHIM in 1911. I have put emotional convulsions more or less within quotation marks, as convulsions are in fact rather seldom observed. The older term, suggested by NEUMANN, »Wegbleiben», in my opinion better corresponds to what really happens. The small child gets into a temper for some reason, often quite unimportant, it reacts on some adversity, a toy is taken away, it is not permitted to have its own way, or it may have had a fall and hurt itself. From pure rage, as it would seem, the child then begins to shriek violently, becomes tense, throws himself in the floor, and may even exert itself so much that it loses its breath for a moment and becomes cyanotic; it may become unconscious for a short while, and convulsions sometimes set in. During these attacks clear signs of a direct deadly fear of suffocation can be observed, the child looks desperately round, waves his arms and kicks wildly during the progress of cyanosis. Unconsciousness sets in rather as a deliverer.

A common explanation of the onset of unconsciousness and convulsions is that the child shrieks so violently and for so long that a hyperventilation alcalosis sets in. The hyperirritability,

which accompanies the alkalosis, should cause the convulsions in children with a corresponding disposition. It will be shown below, however, that this explanation is not sufficient.

As for the start of the proper attack, IBRAHIM is of the opinion that it is based on a pathological determined reflex. We all know that a child may provoke an attack to get his own way. If such a mechanism once has been put into action, the child soon loses its command of it, and a pathological, determined reflex develops. The stimulus is the emotional shrieking, and that this causes a convulsive innervation of the breathing musculature is connected with the pathological state of the nervous system of the child in question. — A violent scare may cause a loss of breath even in a normal subject. In small children a very violent shrieking may become convulsive in character (»loss of breath«). From such states, which appear massed in neuropaths, a determined reflex develops which precipitates a convulsive inspiratory arrest of respiration (sometimes with glottal cramp). So far IBRAHIM's explanation seems to hold.

But how shall we explain the physical background during the rest of the attack? Why does the child lose consciousness? — I have had the opportunity of witnessing a situation with »Wegbleiben« during such circumstances, that it made me examine a bit closer how children of this type behave. This was done at the Children welfare centre of Hälsingborg, where children in the first years of age are well represented.

I had then the immediate impression that the course during the rest of the attack has nothing to do with hyperventilation. The ordinary child is observed to cry from fright or bad temper for any length of time without becoming in the least affected by it except for a heightened colour. On the other side we have these temperamental children, who, in their violent fits of temper, intend to shriek as much as they possibly can. But they do not get far. As early as after a couple of shrieks or even after the first deep inspiration they stop short, so that they remain at the top of the inspiration or just after the beginning of the expiration, and the mechanism locks. They want to shriek but are unable to. — The question of when the respiration stops has

been answered in various ways. According to NEUMANN, IBRAHIM, STIER, FINKELSTEIN, GLANZMANN, and HOMBURGER the arrest of respiration follows on the inspiration. — In Pfaundler-Schlossman's manual GÖTT says, however, that the child when shrieking stretches the expiration so far that it sort of forgets to breathe at the right moment and thus comes in some way »hinter den Atem». The same explanation is also given by PEIPER, who according to his own words after many years of experiments finally succeeded in registering the movements of the diaphragm during the attack in an 8-month-old infant, who finished off the attack with a deep inspiration.

These varying data mainly indicate that the point of time in question is not absolutely fixed in relation to inspiration or expiration. GÖTT's theory cannot be considered to cover all cases, however. Some instances have been described where the children did not have time to begin shrieking (i. e. they had no time for an expiration) but only made a deep inspiration when the affect put a stop to the sequel.

What may happen afterwards is seen from the following case.

It concerns a small girl, not quite two years old (an only child) who had become unconscious several times earlier in connection with outbreaks of temper. At the examination, which was performed in connection with a visit to the home, the child would not sit still on her mother's lap, and when the mother took a steady grip on her just as I was listening to her heart, the child got one of her usual outbreaks, shrieked a couple of times, stopped up after a deep inspiration, then became first red, and soon afterwards blue-cyanotic. When the cyanosis set in, the rate of the heart slowed up and ceased suddenly and completely for the auscultation: no sounds were heard from the heart. In direct connection with this, the child became pale and sank together unconscious but without any convulsions. The time was controlled on a wrist watch with the stetoscope on her heart, and after about 12 sec. the heart beats could be heard again. The rate then accelerated very rapidly in connection with the child's waking up and beginning to cry »ordinarily».

At the Child Welfare Centre I have, during the last 6 months,

had the opportunity of controlling the heart rate of 10 children in affect. None of these cases progressed as far as unconsciousness, however, before the child so to speak got loose and began to cry. In all cases a marked decrease of the heart rate was found, however; in 7 of the 10 cases to about 40 or less. 5 of the children got as far as a real blue cyanosis, all of them showed a very low heart rate, below 40 (in one case the action of the heart had practically ceased for the auscultation). In 3 cases where the heart rate fell to between 60 and 70 during the arrest of respiration it rose immediately to about 180—200 when the children began to cry again.

The phenomenon might be explained in the following way: the child performs a regular or modified Valsalva's experiment. It tries to expire after a preceding deep inspiration, at which the intrathoracic pressure rises. This greatly increased pressure exerts a determining influence on the circulation.

It is as good as proved that the shadow of the normal heart diminishes continuously during a continued Valsalva's experiment, which, as has been stated, is caused by a real diminution of the heart when it is pressed empty. MOSLER and KRETSCHMER (1924) were able to demonstrate, that the shadow of the heart diminishes sooner in children, so that their heart may be empty already after 3—4 heart beats. The heart muscle in children is, as we know, much less constant as regards shape than that of adults. — This diminution of the heart during Valsalva's experiment acts to the same extent on all four chambers of the heart (NOLTE 1934, 1937). Valsalva's experiment has also been labelled the only method of emptying the heart in man.

The output of the heart stroke volume decreases more and more during Valsalva's experiment, and may fall to 0. MOSLER and KRETSCHMER (1924) have investigated the blood pressure in children during Valsalva's experiment, and were able to prove, that this had fallen to 0 only a few heartbeats after the beginning of the experiment. GRIMES found that the blood pressure always falls to 0 during the experiment. By measuring the rate of the pulse wave some investigators were able to draw the conclusion that the circulation can be quite suspended in the region, which

is exposed to the pressure. It has also been observed that, during a regularly performed Valsalva's experiment, the pulse disappears completely in the radial artery. The heart beats empty. In children it is sufficient with a pressure for 5—12 sec. to obtain suspension of the pulse in the radial artery (MOSLER and KRETSCHMER, 1924). According to electrocardiographic investigations this need not imply that the heart ceases to beat (BÜRGER, 1921).

As for the pulse rate the findings do not correspond completely. It seems as if both tachycardia and bradycardia might occur. As far as I know, no investigations in this respect have been performed on children. — By examining the capillaries microscopically BÜRGER (1925) found that a considerable slowing up of the blood stream in the capillary vessels soon sets in. It has further been proved roentgenologically that the pulmonary areas grow lighter during the pressure, which has been interpreted as a beginning emptiness of blood in the pulmonary capillaries.

As mentioned above, electrocardiograms at Valsalva's experiment have shown that the contractions of the heart may continue although the pulse cannot be felt any longer (BÜRGER). In a great material of electrocardiograms of sound subjects performing Valsalva's experiment, BORST (1935) found disturbances in more than 20 % of the investigated subjects, extra systoles, auricular blocking, disturbed leads, and changes of the origin of the stimulus. The auricular block, which occurs only in the pressor phase, causes an insufficient filling of the extrathoracic blood vessels and may in this way cause an anaemia of the brain with an ensuing loss of consciousness and even epileptiform convulsions as a consequence of the onsetting anoxaemia. In connection with Valsalva's experiments it has also been possible to prove electrocardiographically a definite arrest of the action of the heart for up to 24 sec. Sudden death from acute over-exertion has by some authors been explained in this way. BÜRGER (1925) therefore tries to dissuade such people from heavy exertions the peripheral pulse of whom disappears rapidly during a pressure. He further suggests a possible connection between the influence

of Valsalva's experiment on the circulation and accidents at diving or swimming under the water.

Unfortunately I cannot offer any objectively registered cases of »Wegbleiben» to demonstrate the action of the heart and the pulse during the affect. The nature of the affect implies that it must be due entirely to chance if one succeeds in such a registering. Attempts have been made to register the heart electrocardiographically during such a fit of temper. But quite special circumstances must be at hand to precipitate such an attack, and they do certainly not set in on demand. We made attempts with an extremely labile child of 4 years, who was sent to hospital to be observed on account of frequent attacks, which were found to be typical instances of »Wegbleiben». During his stay here it was simply impossible to get him into an affect-bound state. He did not react, when we put him into the electrocardiograph apparatus, we took a blood test in his arm vein without any protests, we brought his mother, whom he had not seen for a week, into the room, but he did not move a muscle. We had the very strong impression that only chance may make it possible to obtain an electrocardiogram in these typical affect states. It is quite sufficiently difficult to have the stethoscope at hand at the very moment the attack sets in; the whole thing is over fairly quickly. In this connection I should like to point out, that the figures for the pulse rate, given above, must be regarded as approximate.

I should like to suggest, however, that the course of these affect states and that of Valsalva's experiment present so many similarities that we are entitled to suggest — even without any objectively registered proofs — that quite comparable mechanisms may be at work in both cases, and that a pressure on the heart to emptiness together with a stopped-up circulation may explain the onset of unconsciousness and the convulsions which sometimes appear in that affect state which has been called »Wegbleiben».

References.

- BORST, W.: Die Veränderungen der Herzschlagfolge bei akuten pressorischen Anstrengungen. *Kliwa* 1935, 14, p. 1821. — BÜRGER, M.: Ueber die klinische Bedeutung des Valsalvaschen Versuches. *Münch. med. Wschr.* 1921, 68, p. 1066. — —: Der Wert des Valsalvaschen Versuches als Kreislauf-

belastungsprobe. Verh. d. deutsch. Ges. f. inn. Med. 1925, p. 282. Quoted from Liedholm. — FINKELSTEIN, H.: Lehrbuch d. Säuglingskrankheiten. Berlin 1921, p. 524. — GLANZMANN, E.: Einführung in die Kinderheilkunde. Berlin 1939, p. 481. — GÖTT, T.: Hdb. d. Kdhk. by Pfaundler and Schlossmann, 4, p. 451. — GRIMES, E.: Effect of Intrathoracic Pressure on Arterial Tension. Arch. int. Med. 47, p. 876. — HOMBURGER, A.: Vorlesungen über Psychopathologie des Kindesalters. Berlin 1926, p. 759: Die respiratorischen Affektkrämpfe. — IBRAHIM, J.: Ueber respiratorische Affektkrämpfe im frühen Kindesalter (das sog. »Wegbleiben« der Kinder) Ztschr. f. d. ges. Neurol. u. Psych. Original volume 5, p. 388. — LIEDHOLM, K.: Studien über das Verhalten des Venendruckes beim Valsalvaschen Versuch. Act. Med. Scand. Suppl. CVI, 1939. — MOSLER, E. and KRETSCHMER, M.: Ueber den Tonus des kindlichen Herzmuskels. Kliwa 1924, 3, p. 2096. — NEUMANN, H.: Ueber das Wegbleiben kleiner Kinder. Arch. f. Khk. 1905, 42. — NOLTE, F. A.: Fortschr. auf d. Geb. d. Rtgstrahl. 1934, 50, p. 211 (quoted from Liedholm). — —: Fortschr. auf d. Geb. d. Rtgstrahl. 1937, 56, p. 20 (quoted from Liedholm). — PEIPER, A.: Das »Wegbleiben«. Mtschr. f. Khk. 1939, 79, p. 236. — STIER, E.: Slg. Abh. neuropath. Kindesalt. 1918, I, 6. (Quoted from Peiper.)

FROM THE ROENTGEN DEPT. (CHIEF: P. NATVIG) AND THE OBSTETRIC
DEPT. (CHIEF: DR. S. KJELLAND MÖRDRE), DRAMMEN HOSPITAL, NORWAY.

Atresia oesophagi congenita with oesophago-tracheal Fistule.

By

P. M. KJELLAND.

Congenital malformations of the oesophagus are probably more common than has hitherto been recognized. It is possible that many infant deaths which have been ascribed to traumata during delivery are due to an undiagnosed congenital oesophago-tracheal fistule.

According to Strong and Cummins the following developmental anomalies are found in the oesophagus:

Total: Stenoses, total atresia, completely lacking anlage, double anlage.

Partial: Stenoses (solitary or multiple), atresia (either in a limited region or as a result of a fold or membrane formation), partially lacking anlage, fistule formation to the trachea or the main bronchus (either with an otherwise normal oesophagus or with a perpendicular oesophagus), double anlage in a limited area, diverticula, cysts.

Of these, fistule formation to the trachea or the main bronchus is the most frequent. Mackenzie compiled 62 cases, 66 % of which had oe.-tr. fistules, Hacker and Lotheissen 223 (77 % with oe.-tr. fistules), Rosenthal (1931) 255 cases (84 % with oe.-tr. fistules). Since then 7 additional cases have been reported.

The clinical picture varies but little from case to case. Sometimes nothing is noticed on the first day. A flow of foamy saliva is often the first clinical observation. Attempts to administer nourishment lead to regurgitation through the nose and mouth. Difficulties in respiration arise partly because the upper air passages are filled with the liquid

nourishment, partly because the bloated upper oesophagus sac presses against the trachea (Selander). The child ceases to drink, its glance becomes fixed and staring, cyanosis and coughing occur. Drowning may result at this point, but the fluid is usually drained through the fistule. There is loss of weight and dessication. The fontanelle becomes insunken, the skin dry and parchement-like. The epigastrium swells up, especially in cases of oe.-tr. fistules. Meconium is excreted per rectum the first few days, later the feces consist of gall-colored slime (hunger feces). The vomit may contain meconium, in which may be seen lanugo hairs and epithelial remains from the swallowed embryonic fluid. The temperature may rise as death is near as in inanition and lung complications.

According to Hirsch in 66 cases death occurred in:

- 15 the 1st day,
- 18 » 2nd,
- 13 » 3rd,
- 14 » 4th,
- 12 » 5th,
- 7 » 7th,
- 6 » 8th,
- 4 » 9th,
- 3 » 10th,
- 4 » 11th,
- 1 » 12th, 13th and 14th days.

5 were stillborn.

Case history:

Born 10/1-43. Normal delivery. Weight at birth 2160 g. Length 47 cm. 12/1 5 vomitings. Constant regurgitation when fed with accompanying cyanosis. Abdomen swollen. Subsequently daily vomiting. Dry lips. Loss of weight and dessication. Roentgen examination with barium sulphate suspension 14/1: oesophagus has a blind end at the level of the 4th thoracic vertebra. The cul-de-sac is half moon shaped at its lower limit. The ventricle and intestine extended with air, indicating communication between the air passages and the digestive tract (Fig. 1).

The child lived for 5 days.

Autopsy: The organs of the chest and throat were removed in toto. The cul-de-sac of the upper oesophagus was 7 cm in length measured from the root of the tongue and was about the size of a little fingertip. The lower part of the oesophagus where the cardia was barely visible was 3 cm in length and about the thickness of a pencil. It pointed conically upward with transition to the oe.-tr. fistule, which ended in the bifurcation. The fistule could be passed by a knobbed probe. There were small, hypostatic broncho-pneumonic foci in the left lung (Fig. 2).

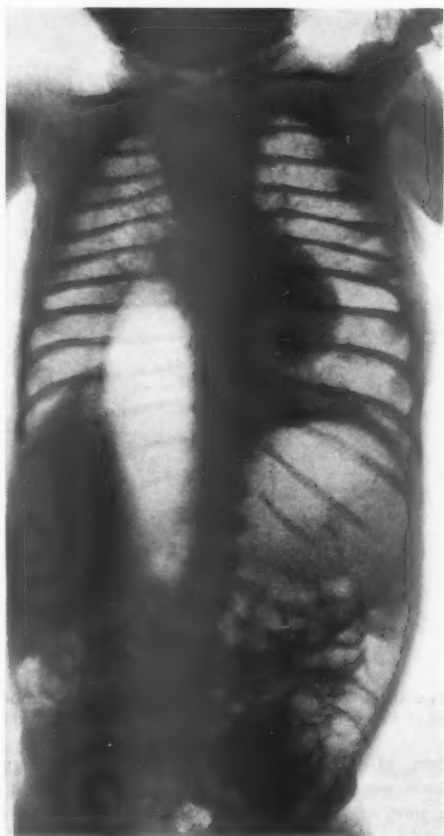


Fig. 1. Upper oesophagus cul-de-sac filled with contrast. Stomach and intestine extended with air.

Histological examination: Sections from the upper cul-de-sac and the lower part of the oesophagus revealed a many-layered squamous epithelium and bundles of cross-striated muscle fibres, from the oe.-tr. fistule partly many-layered epithelium, partly many-layered cylinder epithelium and irregularly arranged, slime-producing gland alveoli (salivary glands). On the whole the picture in this region resembled the situation in the trachea.



Fig. 2. The preparation seen from behind. *a* cul-de-sac of the upper oesophagus, *b* oe-tr. fistule with even transition to the lower part of the oesophagus.

Post mortem, after binding of the duodenum, the stomach and its afferent passages were filled with a suspension of barium sulphate, so that the lower part of the oesophagus, the oe-tr. fistule with its outlet in the bifurcation, and the air passages were clearly visible on the roentgen picture. The upper cul-de-sac was filled from the introitus laryngis (Fig. 3).

The oesophagus and the trachea develop from the anterior intestine. In embryos of 3—4 mm in length there is a longitudinal furrow which shapes the 0-formed lumen of the anterior intestine to an hourglass form. Gradually the folds on the inside come in contact with each other and finally grow together. Just before the formation of this fold the first lung anlage arises as

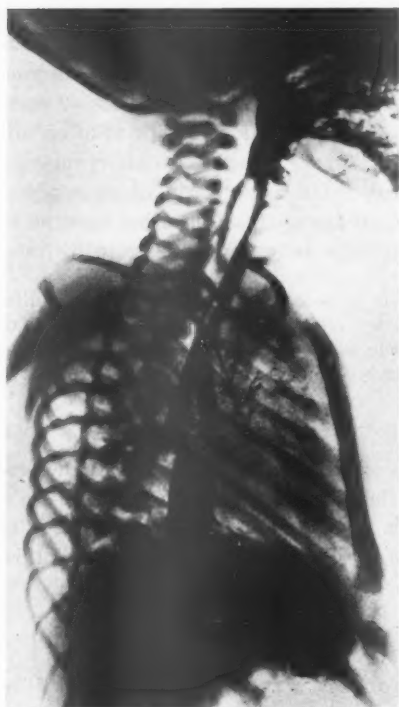


Fig. 3. The stomach, the lower part of the oesophagus, the oe.-tr. fistule, the air passages and the upper oesophagus cul-de-sac filled with contrast. The fistule has its outlet in the bifurcation.

two diverticulum-like sacs anteriorly. Thus two lumens arise, one posterior in connection with the anterior intestine, and one anteriorly which has a blind end. At the end of the 1st embryonic month the narrowing off ceases in a cranial direction where there is communication between the respirational and digestive tracts, later the introitus laryngis.

However the anomaly must be regarded in connection with the frequent multiple defects seen in these children. Thus in 94 cases Plass found that 59 had other anomalies, usually atresia

ani (24 cases). An incomplete separation of the oe.-tr. is therefore not sufficient explanation. Attempts to explain the anomaly on the basis of lacking canalization of an embryonically normal atresia or by pressure from the surroundings (vessels, heart) are difficult to accept. Rosenthal's assumption of an inferior developmental capacity is more acceptable (embryoplastic dysplasia) although the mechanical explanation which is represented by the lacking division of the anterior intestine must be of considerable significance, and especially of great descriptive value.

The prognosis is poor. Operation may prolong life some days or weeks. Gastrostomy alone is contra-indicated because of regurgitation through the fistule, it should be combined with a closing of the cardiac end of the stomach. Jejunostomy has also been tried.

Summary.

Report of a case of congenital atresia of the oesophagus. The upper part of the oesophagus ended in a cul-de-sac at a level with the 4th thoracic vertebra. From the lower part of the oesophagus a fistule led to the bifurcation. As a result of this the digestive tract was filled with air.

Résumé.

Rapport d'un cas d'atrésie congénitale de l'oesophage. La partie supérieure de l'oesophage se terminait en cul-de-sac à la hauteur de la 4^{ième} vertèbre dorsale. De la partie inférieure de l'oesophage, partait un canal fistuleux qui allait jusqu'à la bifurcation. A cause de cette fistule, le tube digestif était fortement gonflé d'air.

Zusammenfassung.

Beschreibung eines Falles von angeborener Atresie des Speiserohres. Der obere Teil des Speiserohres endete mit einem »cul-de-sac« auf der Höhe des 4. Thoracalwirbels. Von dem unteren Teil des Speiserohres führte eine Fistel zu der Bifurcation. Dadurch wurde der Digestionstractus mit Luft gefüllt.

References.

1. BRENNEMANN: Am. J. D. of Children 5: 259, 1919. — 2. —: Am. J. D. of Children 16: 143, 1918. — 3. GAGE and OCHSNER: Ann. Surg. 103, 1936. — 4. HACKER and LOTHEISEN: Neue Deutsche Chir. 1926, Vol. 34. — 5. HIRSCH: J. A. M. A. 76: 1491, 1921. — 6. MACKENZIE: cit. Strong and Cummins. — 7. PLASS: cit. Rosenthal. — 8. RICHTER: Surg., Gynec. & Obst. 17: 397, 1913. — 9. ROSENTHAL: Arch. Path. 12: 756, 1931. — 10. SELANDER: Act. Rad. XXII: 802, 1941. — 11. STRONG and CUMMINS: Am. J. D. of Children 47: 1299, 1934. — 12. SUSMANN: Am. J. Roentgenol. 26: 894, 1931.
-

FROM THE CHILDREN'S WARD OF THE COUNTY HOSPITAL, BORÅS
(HEAD: B. SÖDERLING M. D.), AND THE SAMARITEN CHILDREN'S HOS-
PITAL, STOCKHOLM (HEAD: DOCENT N. MALMBERG).

Contribution to the Literature on Thermo-regulation.

**With special reference to two infants with deformity
of the brain.**

By

S. URWITZ.

In the children's wards at the Borås County Hospital there has recently been encountered a most unusual case of hydrocephalus in which there were interesting vegetative signs relative to temperature regulation, metabolism, and circulation. The regulation of these processes by the brain was completely suspended. The normal method by which these particular processes is regulated is well known, but a brief recapitulation would not, perhaps, be out of place here. Another case displaying suspension of the ability to regulate temperature has been treated at the Samariten Children's Hospital in Stockholm.

In experiments on animals, it has been found that to separate the spinal medulla from the rest of the central nervous system by severing the marrow in the topmost segment of the neck results in total paralysis of all the skeletal muscles except those of the face, which are innervated from the brain. In addition, the respiratory muscles become paralyzed unless the cut is made below the third or fourth cervical segment where the phrenic nerve originates. Complete anesthesia also develops. Among other important consequences may be mentioned the production of a poikilothermic state; the body temperature drops, and if precautionary measures are not taken the body assumes the temperature of the environment. There also occur a number of other signs relative to respiration and circulation. In common with

the other features they make it impossible for the animal to survive.

On the other hand, if the central nervous system is divided through the superior corpora quadrigemina the animal thus decerebrated can survive. It lives wholly under the influence of the spinal marrow, the cerebellum, and the brain stem without the central ganglia. The first-mentioned case of hydrocephalus was an almost perfect example of this type of severance. Nevertheless, the infant lived for several months, and in all probability could have continued to live for a long time through the application of a few simple measures such as a hotwater bottle and occasional paracentesis for the removal of cerebrospinal fluid.

A decerebrated animal seems to lie in a stupor. It lacks conscious motor and sensory functions and thus does not react to its environment. It breathes, however, and it is also capable of adapting its breathing to the demands of the moment. Further, the blood pressure and the minute volume are normal. On the other hand, the power to regulate the temperature is entirely absent. The animal gradually adapts itself to the temperature of the environment and dies if this is too low. The lower borderline temperature for dogs and cats is $+27^{\circ}$ C. Human beings can survive after having been down to $+20^{\circ}$ C. for a short time. The latter fact has been established in persons suffering from exposure.¹ I have been unable to find any other statement regarding the minimum figure for chronic hypothermia. The present case possibly furnishes an answer on that point.

It is obviously impossible for a decerebrated animal to take food unaided. The whole condition has been compared to that existing in narcosis, where heat regulation is also disturbed to a considerable extent.

The above-mentioned severance of the central nervous system leads to loss of the heat-regulating capacity. Severance of the brain further up is hardly possible to carry out, but both by the experimental method and in clinical examinations (slow-growing tumors) it has been established that the temperature

¹ In the mentally deficient a temperature of $29-31^{\circ}$ C. has been recorded over a period of up to one week. (Dedichen, Orsberg.)

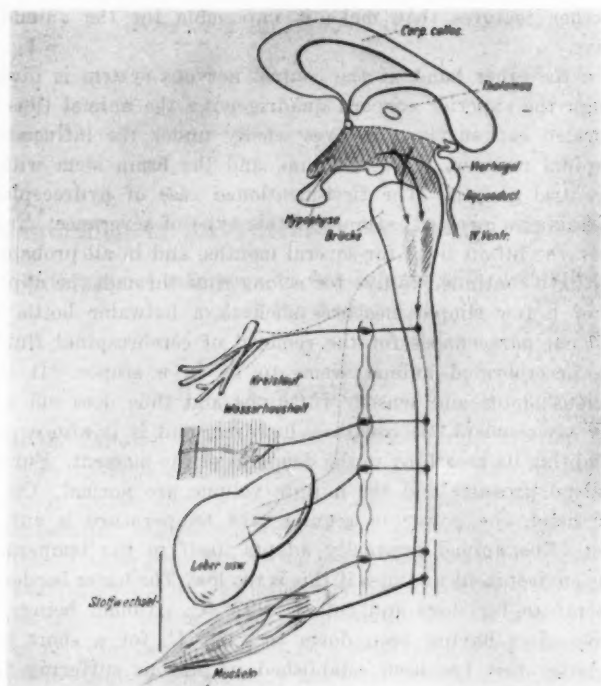


Fig. 1. The sympathetic nervous system. (From Rein, H. *Physiologie des Menschen*.)

sense is situated in the hypothalamus, where centers controlling water metabolism and vasomotor functions are also to be found. Animals with no cerebrum are known to possess the power to keep their body temperature normal. In man, when a temperature center deteriorates gradually other parts of the brain may possibly take over its rôle.

As may be seen from the figure, the temperature is regulated not only from the central nerves. The part marked with double lines shows the gray substance in the lower part of the walls and the floor of the third ventricle together with the aqueduct; in other words, the subthalamus and the hypothalamus. It is

from here that the central heat regulation takes place. In addition it is usual to speak of a chemical and a physical heat regulation. The chemical process consists in an active production of heat through oxidation in the entire muscular system, the liver, and other organs. Thus, the blood in the renal veins is 0.1 degrees warmer than the aortal blood, while the venous blood in the liver can be a few degrees warmer, due to the specifically dynamic action of the food, through which warmth is liberated to the organism. Shivering is an extreme example of the heat production of the muscles. The physical heat regulation functions through the circulation, water storage, and respiration, as for example, through the regulation of the blood flow in the skin, sweating contra goose flesh, and dyspnea during exertion, the latter being also one way in which the body liberates heat. As an illustration of the heat-regulating property of the superficial circulation it can be mentioned that if fomentations are laid direct on the skin and kept for a long period at 50° C. the temperature at a depth of 6—8 mm only rises 2—3° C. It is thus quite impossible, for instance, to supply heat to the abdominal organs by this means. The effect which is nevertheless obtained is believed to be due to a viscero-cutaneous reflex.

On Aug. 9, 1944, a one day old boy was transferred from the maternity wards to the children's department at the Borås Hospital, because the day after birth he appeared listless and sickly. He did not suck the breast. The mother was an unmarried primipara and the report from the maternity clinic was that she seemed to show no particular interest in her child. She also appeared to be slightly mentally defective. The birth had been normal.

The infant had weighed 2560 g at birth, or slightly more than the weight regarded, on the basis of statistics, as indicative of congenital debility. He had been born seven weeks before term. According to the reports he seemed lively on the first day of life, was a good color, and had a strong cry. The circumference of the head was 36 cm.

On admission to the children's ward 24 hours after birth his skin was normal in color. His cry was weak. There was slight edema on the backs of his hands. No abnormal signs were obtained from the internal organs. On Aug. 10 petechial hemorrhage was observed on the left thigh and the right shoulder. The same day an unusual and disturbing reaction occurred. When blood was being withdrawn for a

prothrombin determination the usual warm foot-bath was given, the temperature of the water being controlled by the nurse (in this case the head nurse of the ward), who held her hand in the water. The temperature was estimated to be 42° C. The foot-bath, which was continued for five minutes, did not have the desired effect; only an infinitesimal amount of blood was obtained. One hour after the foot-bath several blisters appeared on the toes. The following day the skin on his feet and legs, up to a sharply defined line 2 cm above the malleoli, was bright red, with a cyanotic tinge. On his feet there were now a number of pea-sized, serous blisters as well as remains of similar blisters. The outer phalanges of the toes were strongly cyanotic. Later in the day the feet began to swell. These skin lesions gradually took on the appearance of those seen in third degree burns and frost-bite. The end result was necrosis and loss of the terminal phalanx of the second toe on the left foot and also of the tips of all the other toes, which all lost their nails.

On Sept. 4, he was discharged, after having shown a normal gain in weight and a normal temperature during his entire stay at the ward. He was slightly anemic but he was lively, and was being reared solely on the breast. His skull and internal organs were normal. A diagnosis of Raynaud's disease (?) and congenital debility was made.

On Oct. 23, at the age of 2½ months, he was brought to the outpatient service, and was reported to have been well, increased to 4 000 g, and caused no anxiety until Oct. 20. He had then suddenly turned «as cold as ice», although no difference had been made in his habits. When examined, he was found to be slightly listless, but he was a good color. His temperature was 36.2° C. and his skin was doughily edematous.

From that time onwards he needed a hotwater bottle, but no other abnormalities were observed. After a while, a high degree of craniotabes developed and his head began to increase rapidly in size. He was therefore admitted to the hospital for observation on Dec. 9. He was found to be in good physical condition, weighing at 4 months old almost 6 kg. His skin was normal in color. He was mentally backward, could not balance his head and did not follow objects with his eyes. The circumference of his head was 46 cm as compared with the normal maximum figure of 40 cm. With regard to the skeleton it is recorded that there was maximal craniotabes over all the bones of the skull except the occipital bone and the lower part of the frontal bone. The bones were so soft that they did not give the impression of being bone at all. The entire calotte felt like parchment.

With a view to making further investigations (blood calcium, and so on) a sinus puncture in the fontanelle was tried but was unsuccessful. All that was obtained was fluid at high pressure. An encephalographic examination was attempted with the usual neck puncture but only a

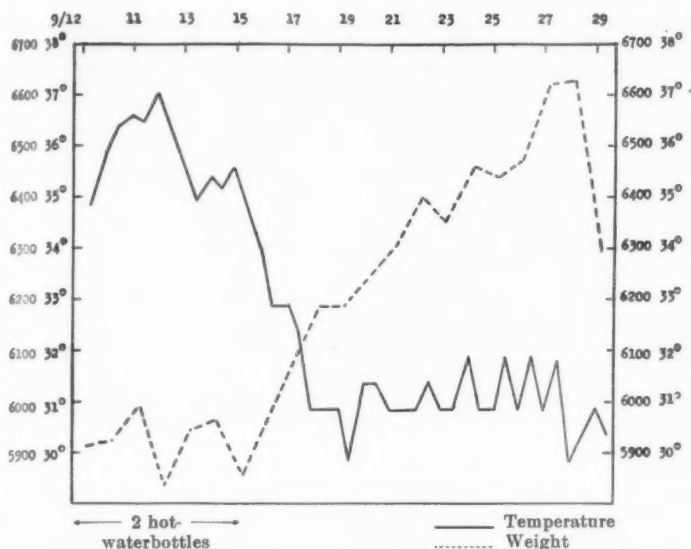


Chart 1. Temperature and weight in case 1.

small amount of very bloody fluid could be withdrawn, and the experiment was therefore discontinued. Two days later a lumbar puncture and a neck puncture were done but the results were again negative. Immediately after this, a puncture into the fontanelle was undertaken, 60 cc. of clear fluid being withdrawn and a corresponding amount of air injected. Thus, there must have existed an absolute obstruction between the cavities of the brain and the lumbar part of the canal. Roentgen examination (Hagberg) revealed enormous dilatation of the lateral ventricles and a small third ventricle. There appeared to be very little brain substance left. The roentgenologic diagnosis was internal and external hydrocephalus.

In view of the roentgen findings it was decided to withdraw the hotwater bottle. Even if the child were to survive there was no chance of saving the brain. The water bottle was withdrawn on Dec. 15, and his temperature gradually dropped. On Dec. 18 it was 31° C., and it subsequently never rose beyond this. His general condition was still good, however. His listlessness increased and he became more and more difficult to feed. Nevertheless, he continued to gain well because of the retarded metabolism.

An attempt was made to measure the metabolic rate but the result

was unsatisfactory owing to lack of equipment. An electrocardiogram showed an unusually long interval between the QRS complexes and the T waves; thus, the same abnormality as is seen in spasmophilia. The Wassermann reaction in the mother was negative. All the blood counts carried out yielded normal values. Unfortunately, only blood counts by microdetermination could be made. The sedimentation rate (microdetermination) dropped from 40 mm to 16 mm per hour. On Dec. 28, another encephalogram was made, 100 cc. of fluid being tapped. The fluid showed the same conditions as before. The next day, he had petechial hemorrhage all over his body, was more listless than ever, and died the same evening.

At autopsy, the skull was found to be literally filled with fluid and contained only rudiments of a brain (fig. 2). *Pathologico-anatomic diagnosis* (Reuterwall and Hansson). As regards the gross appearances it is reported that there was a fairly high degree of internal hydrocephalus embracing both the lateral ventricles and the third ventricle. The midbrain was relatively large; in section it seemed to be almost egg-shaped owing to the fact that the cerebral peduncles were not apparent. The aqueduct of Sylvius was not visible to the naked eye in the apparently gliomatous tissue. The fourth ventricle was of normal width and configuration; its fourth recess seemed blind. Microscopic appearances: In sections from the midbrain, taken at the site of the aqueduct of Sylvius, a number of gland-like lumen formations lined with ependymal cells were observed. Fairly wide-spread gliomatosis was present. Both in the midbrain and in sections from the reduced substance in the hemispheres there were fairly pronounced inflammatory lesions in the form of round cell layers around the vessels and diffuse infiltration of round cell and fibroblastic elements. Immediately adjoining the fourth ventricle there were collections of calcium deposits in the parenchyma. In the choroid plexuses the connective tissue was somewhat increased, the capillaries were distended with blood and there was a moderate degree of diffuse round cell infiltration. In places, there were macrophages containing hemosiderin, and calcium deposits were also present. The soft membranes were fairly extensively infiltrated with round cells and slightly fibrotic. No micro-organisms could be observed in the Gram-stained sections. Nor was there anything to indicate specific inflammation. It was not possible to decide with certainty whether the changes observed in the mesencephalon — »splitting-up» of the aqueduct of Sylvius, and gliomatosis — were an actual deformity or whether they had arisen as a consequence of the inflammatory lesions. Judging from the findings, the former possibility seemed the more likely one. The diagnosis made was meningo-encephalitis of non-specific type, internal hydrocephalus embracing both the lateral ventricles and the third ventricle, and malformation of the midbrain.

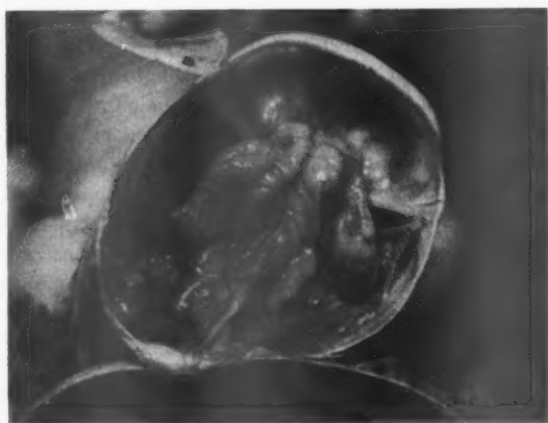
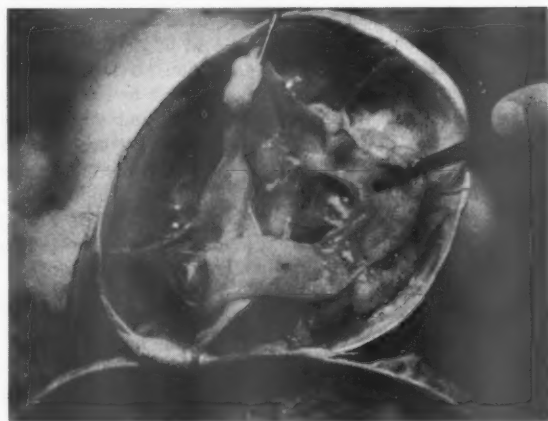


Fig. 2. Case 1. a) The brain *in situ*.



b) The brain opened up.

Thus, in this infant, there was an obstruction between the ventricles and the lumbar part of the canal, causing among other things destruction of the heat centers. As is well known, a vasomotor center is believed to exist in close proximity to the heat

center. There seems good reason to assume that the explanation of the vasoconstrictory effect and the gangrene in the toes which occurred as a result of the warm foot-bath is to be sought in the lesion in the central regions of the brain. The gain in weight was in all probability due to the retarded metabolism, but it might also be connected with the fact that the center for water metabolism is situated in the corresponding part of the brain.

The case might be described as a physiologic experiment by Nature on a decerebrated human being, and it demonstrates that the vital processes can proceed normally at a temperature of 31° C., at least for as long as 14 days.

The other case in which the power to regulate temperature was suspended was a girl aged one month at the time of her admission to the Samaritan Children's Hospital. She had weighed 2900 g at birth, and was the second child of a healthy, 26 year old mother. The birth had been completely normal. During the infant's stay at the maternity hospital, where the temperature had remained almost continuously at 35.6° C., nothing unusual had been observed, but after her arrival home her temperature was abnormally low. On Apr. 3, 1945, her temperature was 35.2° C. and on the morning of admission no temperature at all was recorded, despite the fact that she appeared to have a cold. She had thrown up the whole of the 6 o'clock meal and at the 10 o'clock meal refused the breast. On admission her temperature was 33.2° C. and she seemed listless. During the examination she cried continuously. She was pale and fairly thin, and the turgor was slightly decreased. Her weight was 3500 g. Her palate was slightly inflamed. The anterior fontanelle felt tense, bulged slightly, and measured three fingertips in width. It extended in a sagittal direction to the middle of the forehead and laterally down to the same level. The sagittal suture showed a diastasis of 0.5—1.0 cm. The posterior fontanelle measured not quite two fingertips in width. The circumference of the head, which had been 32 cm when she was at the maternity hospital, was now 38.5 cm. A lumbar puncture yielded blood-tinged fluid showing strong protein reactions; there were 27 cells, chiefly lymphocytes, and 1300 fresh red blood corpuscles per cubic mm. The initial pressure was 170 mm H₂O. The prothrombin index was normal. During the stay in hospital she had two hotwater bottles in the bed and a radiator in the room but the temperature pendulated between 35° and 39° C. (chart 2). During the first days in hospital she vomited repeatedly and had ugly-looking stools. It was not until Apr. 11 that the stools became normal and after that the vomiting also ceased. Her weight rose from 3500 g, on

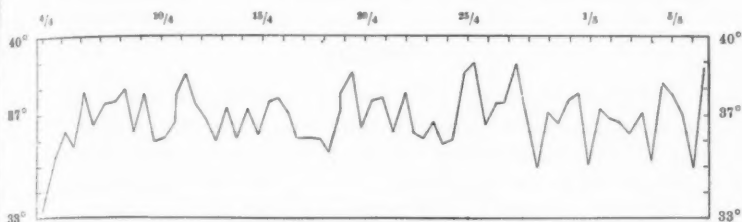


Chart 2. Temperature in case 2.

the day of admission, to 4 040 on May 4, but she had to be fed with a catheter the whole time as she was too listless to suck. During this month her head increased only 1 cm in circumference and her general condition remained the same as it had been on admission. Ventricular puncture was done twice and on both occasions the fluid obtained was lemon-yellow, with strong protein reactions and about 50 cells. She died on May 6, apparently from pneumonia.

Autopsy revealed a skull of normal size but the anterior fontanelle was perhaps slightly larger than normal. The inner surface of the dura mater was smooth, damp, and glistening, the fine membranes were thin and transparent with no fluid in the spaces. Here and there, there were small yellowish, turbid and firm areas in the outermost parts of the cerebral cortex at the base of the brain. The lateral ventricles were considerably dilated and full of a clear lemon-yellow fluid. Large firm, yellowish and opaque areas were scattered through the walls of the lateral ventricles. The upper part of the medulla oblongata had assumed a club-shaped appearance. Microscopic examination (Wahlgren) revealed large collections of inflammatory cells, chiefly lymphocytes, around the vessels in the parts of the brain examined. In the brain tissue also, there were many large areas where the tissue was riddled with inflammatory cells, mainly lymphocytes. No signs of tumor were observed. *Pathologico-anatomic diagnosis*: Severe, acute encephalitis.

In this second case also, there was hydrocephalus and a lesion in the medulla oblongata, the upper part of which showed a club-like elevation. In all probability also, the thermotaxic center in the hypothalamus had been destroyed as a result of these two abnormalities, and in addition we have encephalitis, which was observed in the first case also. Thus, in both cases, there was complete suspension of the temperature-regulating power in connection with cerebral changes demonstrable both macroscopically and microscopically.

Summary.

A report is made on two infants with hydrocephalus in whom the temperature-regulating capacity was suspended. In one of them, gangrene in the tips of the toes developed after a warm foot-bath. When no external heat was supplied this infant assumed a temperature of 31° C. and at the same time increased noticeably in weight. In the other infant, which received a constant supply of extra warmth, the temperature ranged between 35° and 39° C. without any signs of infection appearing. In both instances postmortem examination revealed the presence of meningo-encephalitis embracing, among other parts, the midbrain.

References.

- DEDICHEN, H. H., *Nordisk Medicin*, 2: 1840, 1939. — MEYER, H. H., *Klinische Wochenschrift* 14: 962, 1935. — REIMAN, J. A. M. A. 115: 1606, 1940. — REIN, *Physiologie des Menschen*. Berlin 1943. — THAUER, R., *Klinische Wochenschrift*, 20: 969, 1941. — ØRSBERG, H., *Ugeskrift for læger*, 106: 709, 1944.

FROM MRS. C. HERMANSEN'S NURSING HOME. THE COPENHAGEN MUNICIPAL PEDIATRIC DEPARTMENT, MARTINSVEJ, COPENHAGEN.
PHYSICIAN-IN-CHIEF: A. MEYER, M. D.

100 Galactose Tolerance Tests on Children with Unimpaired Livers.

(Normal Values for Children Down to the Age of Two.)

By

E. SELMAR.

It is well-known that BAUER's galactose tolerance test in the case of adults consists of the peroral administration of 40 g of galactose to the subject whose urine afterwards normally should contain a maximum of 3 g galactose. In case of children, on the other hand, very few reports exist indicating the method to be used and the amount of eliminated galactose considered normal.

By way of an example the following test (using the same subject as test D9 in Table I) serves to demonstrate that the dosage and normal values for adults are inapplicable to children: A girl, aged $5\frac{1}{2}$ and weighing 18 kg, admitted for scabies. She had never been jaundiced, and SCHLESINGER's test for urobilinuria was negative (the modification of MARCUSSEN & SVEND HANSEN diluting the urine 1 + 4). The urine proved to contain 6.9 of the 40 g of galactose administered by mouth, i. e. the value was »pathologic». (CHOMET (4) arrived at similar results.)

Considering that the weight of the liver in growing children constitutes a decreasing proportion of the body weight, there is nothing surprising in the results of FABISCH & ETZOLD (1) and HEYMANN & HOWE (2) who found that the carbohydrate tolerance (tested for levulose and galactose) was greatest in infants and later decreasing — the tolerance being expressed in the number of grammes carbohydrate per kg body weight which children can receive without showing traces of it in the urine.

FABISCH & ETZOLD: Newborn 2.2 g/kg, adults 0.6 g/kg. HEYMANN & HOWE: A minimum of 4 g/kg to infants (only 2 of 14 eliminating galactose after the administration of 30 g, whereas 14 out of 16 older children eliminated galactose upon administration of 40 g).

It is presumably in the light of similar results that HALLMANN (3) recommends the following decreasing dosage of galactose according to body weight (age):

Children from $1\frac{1}{2}$ to $2\frac{1}{2}$ years: 2 g/kg.
Children from $2\frac{1}{2}$ to 5 years: $1\frac{1}{2}$ g/kg.
Children from 5 to 9 years: 1 g/kg.
Children of 9 years and more: $\frac{3}{4}$ g/kg, a total of 40 g-adult dosage.

The normal elimination for all ages and body weights is up to 3 g. (There is no statement as to the material used and no reference to the original report.)

According to CHOMET (4) children of a body weight above 16 kg must not eliminate more than 3 g of 30 g administered by mouth. (The tests were carried out on 36 children ranging in age from $3\frac{1}{2}$ to 14 years. A couple of girls, aged 5 and weighing 14 and $15\frac{1}{2}$ kg, however, eliminated 6.7 and 3.5 g respectively.)

MEYER & STERN (5) state that during the first 7 years of life children normally must not eliminate more than 3 of 30 g galactose (and not more than 0.5 g out of 20 g). M. & S. found that the children eliminated extremely varied amounts, without relation to age or body weight. (Their material of 63 children is not, however, a normal material, including i. al. numerous »convalescents» after digestive disorders.)

ASHLEY WEECH (6) advocates the following galactose tolerance test for children: Normally galactose should not be demonstrable in the blood 3 hours after the peroral administration of 1.75 g/kg. (No information is afforded as to the material used and a reference to the original report is lacking. Furthermore, NISSEN (8) has demonstrated that the elimination of galactose is a more reliable standard for the hepatic function than the concentration of the substance in the blood.)

Writer's Galactose Tolerance Tests.

Material: 78 children with unimpaired livers, classified according to sex and age:

- 2— 5 years: 16 boys and 16 girls
- 5—10 years: 23 boys and 15 girls
- 10—14 years: 4 boys and 4 girls

22 of these children were submitted to 2 tests with a different dosage and an interval of at least 24 hours, which period has proved to be adequate to make a reproduction of the results possible. The material only includes children who were able to hold their urine; the enuresis patients used all had been »cured» at the time of the test. The helminthiasis patients were tested while not under treatment. The following conditions were observed in all cases: The temperature was normal, there was no urobilinuria, and no clinical signs of circulatory or resorption disturbances.

Technique. 3 hours before the usual morning meal the child is awakened and made to void his urine which is discarded and the child drinks the galactose mixed with water. The amount of water is about 125 cc. per each 20 g galactose or part thereof. The »fasting urine» of the first three hours is collected in glass I, whereupon the child has his usual breakfast. The test is terminated after the next 3 hours' urine has been collected in glass II. In 50 cases the amount of galactose administered was $\frac{2}{3}$ g/kg body weight (g. purissimum »Sandoz») corresponding to 40 g to adults, and in the remaining 50 cases the amount was 1 g per kg body weight. The elimination of galactose was determined by means of a polarimeter provided with a tube measuring 94.7 mm in length¹ after the urine had been prepared with carbon and acetic acid by the method of GEILL(7). Galactose was not in any case demonstrable in glass II. The results are in conformity with NISSEN's (8) who, submitting 10 children, aged 6—14, suffering

¹ My thanks are due to H. SEEMANN M. D. for the permission to use a »Hellige» polarimeter at the Army and Navy Hospital, Copenhagen.

from catarrhal jaundice to 55 tests using 40 g, only observed elimination after the 3rd hour in the case of 2 children tested 3 times. These 2 children had revealed a pathologic elimination already during the first 3 hours. *A three-hour test, therefore, is sufficient. The necessity of the subject being fasting before and during the test is i. al. evident from a report by NISSEN (9) showing that a meal containing carbohydrate is capable of reducing the elimination of galactose.*

Results. The results are set out in Tables I and II, the $\frac{2}{3}$ g/kg tests and the 1 g/kg tests respectively. As to details the reader is referred to the »statistical remarks», so here the writer merely wants to point out that the statistical analysis of the results, carried out by G. RASCH Ph. D., serves to demonstrate that the results of the 1 g/kg tests allow the fixing of an upper limit for normal elimination, below which limit 95 per cent of all results will be situated. This limit is represented by

$$y = 4.08 x$$

In other words, normal children receiving 1 gramme galactose per kilo body weight usually eliminate a maximum of 4 per cent of the quantity administered.

(No statistical conclusions are derivable from the $\frac{2}{3}$ g/kg tests.)

It appears from the following test (D20) that the writer's modification of BAUER's galactose tolerance test is capable of showing pathologic values: A boy, aged 10 and weighing 29 kilos, with catarrhal jaundice. TAKATA ++, 2 weeks later ÷. MEULEN-GRACHT 40, Urine + urobilin + bile pigment. 7.6 g or 26 per cent of the 29 g galactose given by mouth were eliminated with the urine.

Statistical Remarks.

A striking feature of the material is the large number of children who did not eliminate galactose. When the material is divided into small groups according to the quantity received, which groups form the basis of diagrams presenting the eliminations plotted against their

probits (see IPSEN & JERNE (10)) the points will be grouped around straight lines, an evidence that the eliminations are normally distributed. The great accumulation in elimination 0 is explicable when considering that this normal distribution is »truncated» (see HALD, JERSILD & RASCH (11)). I.e. the normal distribution does not apply to the elimination itself, but to a factor (factors) constituting a condition for the elimination and having an effect which is measured by the elimination, if any. The probit diagrams form the basis of the following calculation of mean value (m) and dispersion (d):

Dosage 1 g/kg				Dosage $\frac{2}{3}$ g/kg			
Quant. adm. (g)	Average dos. (g)	m (cg)	d (cg)	Quant. adm. (g)	Average dos. (g)	m (cg)	d (cg)
$<16\frac{1}{2}$	14.5	7	19.0	$<12\frac{1}{2}$	10.4	$\div 3$	30
$16\frac{1}{2}-22\frac{1}{2}$	19.3	18	37.5	$12\frac{1}{2}-18\frac{1}{2}$	14.6	$\div 12$	68.5
$\geq 22\frac{1}{2}$	28.4	17	43.0	$\geq 18\frac{1}{2}$	(too few observations)		

It is evident that m increases with the dose in the 1 g/kg group, but a more thorough analysis is required in order to decide whether the difference is significant and whether the decrease of m with the increasing dose in the $\frac{2}{3}$ g/kg group is due to pure chance (e.g. on account of an unfavourable grouping of the material). In case of such a thorough analysis a d increasing in both groups with the dose is of decisive significance.

In the primary, normal distribution the mean value (μ) is in linear dependence on the administered dose x :

$$\mu = a + \beta x$$

and the dispersion (δ) is proportional to the dose x :

$$\delta = \chi x$$

The estimation of the position (a), the slope (β) and the dispersion factor (χ), and the mean errors of these estimates prove to be

$a \div 36.7$	$me(a)$	21.4
b 2.74	$me(b)$	1.19
k 1.95	$me(k)$	0.26
Dosage 1 g/kg		

$a \div 19.6$	$me(a)$	27.2
b 1.17	$me(b)$	2.15
k 3.60	$me(k)$	0.59
Dosage $\frac{2}{3}$ g/kg		

Table I.
Calactose administered $\frac{2}{3}$ g/kg.

Date of test	Date of discharge	Initials	Sex	Age	Weight (kg)	Diagnosis	Galactose by mouth (g)	Galactose in urine (cg)	Elimination (p. ct.)	Mark of test	Reference to 1 g/kg test on the same subject
19.9.43	21.9.43	K. J.	m	4	17	Asthma bronchiale	12	0	0	A 3	
20.9.43	4.10.43	R. B.	f	9	24	Vitium domesticum	16	0	0	A 4	
14.10.43	25.10.43	K. M.	m	5½	21	Impetigo	14	0	0	A 7	
10.11.43	25.11.43	O. M.	m	4	20	Asthma bronchiale	13	0	0	A 9	
1.1.44	8.1.44	H. P.	m	13	40	Eauresis nocturna	27	0	0	A 11	
6.7.44	9.7.44	N.-L.	m	3	15½	Ascariasis	10	0	0	D 38	(D 37)
15.9.43	25.9.43	L. B.	m	5	21	Eauresis nocturna	14	0	0	D 4	
19.9.43	3.10.43	M. N.	f	6½	21	Oxyuriasis	14	0	0	D 7	
20.9.43	31.12.43	K. J.	m	4½	15½	Eauresis nocturna	10	0	0	D 8	(D 22)
7.10.43	28.11.43	L. S.	f	4	20	Impetigo	14	0	0	D 12	
5.11.43	10.12.43	I. V.	m	3½	17	Impetigo	11	0	0	D 13	
20.1.44	8.2.44	A. B.	f	12	38	Oxyuriasis	26	0	0	D 23	(D 21)
4.11.43	11.11.43	P. M.	m	5	19½	Impetigo	13	0	0	F 2	
22.10.43	20.11.43	R. T.	f	12½	35	Asthma bronchiale	27	0	0	E 5	
31.12.43	20.1.44	P. C.	m	6½	25	Vitium domesticum	17	0	0	F 11	(F 9)
31.12.43	8.1.44	J. J.	m	5	20½	Commotio cerebri	14	0	0	F 12	(F 16)
3.1.44	14.1.44	P. M.	m	5	15½	Asthma bronchiale	11	0	0	F 13	
3.1.44	22.1.44	M. P.	m	5½	17	Eauresis nocturna	12	0	0	F 14	
7.2.44	31.3.44	A. R.	m	4	21	Eauresis nocturna	14	0	0	F 20	(F 18)
22.2.44	26.2.44	B. S.	f	3	13	Nihil (obs. dyspepsia)	9	0	0	B 2	(B 3)
15.2.44	24.3.44	J. A.	m	4	18	Eauresis nocturna	12	0	0	A 16	(A 18)
18.2.44	20.3.44	C. D.	f	7½	20½	Oxyuriasis	14	0	0	D 25	(D 27)
27.2.44	28.4.44	B. C.	m	2	42						

22.2, 44	26.2, 44	B. S.	f	3	13	Nihil (obs. dyspepsia)	9	0	0	R 2	R 3
15.2. 44	24.3. 44	J. A.	m	4	18	Enuresis nocturna	12	0	0	A 16	(A 18)
18.2. 44	20.3. 44	C. D.	f	7 $\frac{1}{2}$	20 $\frac{1}{2}$	Oxyuriasis	14	0	0	D 25	(D 27)
27.2. 44	13.4. 44	B. C.	m	2 $\frac{1}{2}$	13 $\frac{1}{2}$	Enuresis nocturna	9	0	0	F 21	
28.3. 44	16.4. 44	Q. J.	f	3	17	Enuresis nocturna	11	0	0	D 30	(D 28)
24.8. 44	24.8. 44	J. S.	m	2	14	Impetigo	9	0	0	A 34	(A 33)
8.6. 44	22.6. 44	L. J.	f	8	20	Enuresis nocturna	14	0	0	A 23	(A 21)
28.6. 44	31.7. 44	H. H.	f	3 $\frac{1}{2}$	14	Oxyuriasis	9	0	0	A 27	(A 25)
9.10.43	11.11.43	B. D.	f	2	12	Impetigo	8	6	1	E 1	
28.6. 44	6.7. 44	O. M.	m	4	17	Enuresis nocturna	11	10	1	A 28	(A 26)
1.1. 44	26.2. 44	B. W.	m	3 $\frac{1}{2}$	13	Enuresis nocturna	9	10	1	A 10	(A 12)
20.4. 44	8.5. 44	F. C.	m	6	19	Nihil (obs. asthma b.)	13	11	1	E 10	(E 9)
20.6. 44	24.6. 44	H. O.	f	2 $\frac{1}{2}$	15 $\frac{1}{2}$	Enuresis nocturna	10	14	1 $\frac{1}{2}$	D 36	(D 35)
4.10.43	7.10.43	E. S.	m	10	27 $\frac{1}{2}$	Debilitas mentis	18	15	1	A 6	
8.5. 43	14.5. 43	A. J.	f	10	30	Enuresis nocturna	20	18	1	E 11	
21.9. 43	4.10.43	A. J.	f	5 $\frac{1}{2}$	19	Enuresis nocturna	13	18	1 $\frac{1}{2}$	A 5	
12.6. 44	11.7. 44	J. B.	f	14	35	Enuresis nocturna	23	24	1	F 24	(F 23)
18.2. 44	29.4. 44	B. N.	m	5	17 $\frac{1}{2}$	Enuresis nocturna	12	27	2	D 24	(D 26)
4.10.43	21.10.43	H. M.	f	4 $\frac{1}{2}$	18	Scabies	12	30	2 $\frac{1}{2}$	D 10	
9.9. 43	12.9. 43	K. O.	m	8	25 $\frac{1}{2}$	Oxyuriasis	19	30	1 $\frac{1}{2}$	D 2	
7.2. 44	31.3. 44	T. R.	m	10 $\frac{1}{2}$	32	Enuresis nocturna	21	31	1 $\frac{1}{2}$	F 19	(F 17)
4.11.43	11.11.43	B. M.	m	7 $\frac{1}{2}$	23	Impetigo	15	31	2	F 1	
10.10.43	11.11.43	A. D.	f	4 $\frac{1}{2}$	16 $\frac{1}{2}$	Impetigo	11	33	3	E 3	
11.10.43	29.10.43	P. M.	m	3 $\frac{1}{2}$	16	Impetigo	11	45	4	E 4	
24.2. 44	26.3. 44	J. A.	m	4 $\frac{1}{2}$	19	Enuresis nocturna	13	45	3 $\frac{1}{2}$	A 15	(A 17)
9.10.43	11.11.43	I. D.	f	3 $\frac{1}{2}$	14 $\frac{1}{2}$	Impetigo	10	53	5	E 2	
8.5. 44	9.5. 44	M. O.	f	8	26	Enuresis nocturna	18	75	4	E 12	
8.6. 44	17.6. 44	K. L.	f	9	30	Oxyuriasis	20	90	4 $\frac{1}{2}$	A 22	(A 20)
4.10.43	21.10.43	A. M.	f	5 $\frac{1}{2}$	21	Scabies	14	100	7	D 9	
7.10.43	8.10.43	A. S.	f	7	25	Valvovaginitis	17	100	6	B 1	
9.11.43	20.12.43	L. H.	f	8	21	Enuresis nocturna	14	110	8	F 4	

Table II.
Galactose administered 1 g/kg.

Date of test	Date of discharge	Ini- tials	Sex	Age	Weight (kg)	Diagnosis	Galactose by mouth (g)	Galactose in urine (cg)	Elimination (p. et.)	Mark of test
11.12.43	18.12.43	A. B.	f	5	15	Oxyuriasis	15	0	0	F 8
5.1.44	26.2.44	B. W.	m	3 $\frac{1}{2}$	13	Enuresis nocturna	13	0	0	A 12
11.12.43	20.1.44	P. C.	m	6 $\frac{1}{2}$	25	Vitium domesticum	25	0	0	F 9
17.2.44	24.3.44	J. A.	m	4	18	Enuresis nocturna	18	0	0	A 18
20.2.44	20.3.44	C. D.	f	7 $\frac{1}{2}$	20 $\frac{1}{2}$	Oxyuriasis	21	0	0	D 27
24.2.44	26.2.44	B. S.	f	3	13	Nihil (obs. dyspepsia)	13	0	0	B 3
6.4.44	29.4.44	Y. J.	f	4	17	Anorexia nervosa	17	0	0	E 6
15.3.44	27.5.44	J. L.	m	10	26	Hysteria	26	0	0	A 19
7.4.44	19.5.44	A. F.	f	2 $\frac{1}{2}$	13	Anorexia nervosa	13	0	0	D 31
30.8.44	31.8.44	B. P.	m	2	13	Anorexia nervosa	13	0	0	F 29
19.9.44	13.10.44	A. W.	f	6	19 $\frac{1}{2}$	Enuresis nocturna	20	0	0	A 38
3.8.44	11.8.44	H. F.	m	7	24 $\frac{1}{2}$	Enuresis nocturna	25	0	0	F 28
30.8.44	2.10.44	E. J.	m	5 $\frac{1}{2}$	18	Oxyuriasis	18	0	0	A 36
24.8.44	30.9.44	B. H.	m	6	21	Incont. alvi e obstip.	21	0	0	A 35
27.6.44	6.7.44	I. M.	m	5	16	Enuresis nocturna	16	0	0	A 29
24.6.44	6.7.44	O. M.	m	4	16 $\frac{1}{2}$	Enuresis nocturna	17	0	0	A 26
14.6.44	20.6.44	E. P.	m	9	22 $\frac{1}{2}$	Enuresis nocturna	23	0	0	A 24
11.8.44	24.8.44	J. S.	m	2	12	Impetigo	12	3	0	A 33
9.7.44	25.8.44	J. H.	f	4	16	Enuresis nocturna	16	3	0	D 40
30.4.44	4.6.44	J. J.	m	6	17 $\frac{1}{2}$	Anorexia nervosa	18	4	0	D 32
27.6.44	27.7.44	H. S.	m	3	15	Enuresis nocturna	15	8	$\frac{1}{2}$	A 30
16.6.44	24.6.44	H. O.	f	2 $\frac{1}{2}$	15	Enuresis nocturna	15	11	1	D 36
6.8.44	16.8.44	V. J.	f	4	15	Nihil (obs. obstinatio)	15	14	1	D 32

30.4. 44	4.6. 44	J. J.	m	6	17 ½	18	4	0	D 32
27.6. 44	27.7. 44	H. S.	m	3	15	15	8	1	A 30
16.6. 44	24.6. 44	H. O.	f	2 ½	15	15	11	1	D 36
6.8. 44	16.8. 44	V. J.	f	4	15	15	14	1	A 32
24.6. 44	31.7. 44	H. H.	f	3 ½	14	14	15	1	A 25
23.6. 44	9.7. 44	N. L.	m	3	16	16	15	1	D 37
6.6. 44	17.6. 44	K. I.	f	9	30	30	17	1	A 20
24.3. 44	26.4. 44	Q. J.	f	3	17	17	17	1	D 28
19.9. 44	27.10. 44	J. J.	m	4 ½	16	16	18	1	A 37
6.6. 44	22.6. 44	L. J.	f	8	20	20	19	1	A 21
5.1. 44	8.1. 44	J. J.	m	5	20 ½	21	20	1	F 15
19.9. 44	26.10. 44	K. N.	f	3 ½	16 ½	17	23	1	D 44
9.7. 44	9.7. 44	B. O.	m	7 ½	26	26	25	1	D 41
12.7. 44	14.9. 44	F. T.	f	5 ½	16	16	25	1 ½	A 31
19.9. 44	25.9. 44	N. R.	m	5 ½	23 ½	24	27	1	F 31
3.8. 44	21.8. 44	I. L.	m	6 ½	21	21	32	1 ½	F 27
29.8. 44	10.10. 44	K. V.	f	2	14	14	33	2	F 30
6.7. 44	26.8. 44	E. N.	m	6 ½	20	20	34	1 ½	D 39
19.9. 44	29.9. 44	K. L.	f	2 ½	13	13	35	2 ½	D 43
17.2. 44	26.3. 44	J. A.	f	4 ½	18	18	38	2	A 17
8.4. 44	11.7. 44	J. B.	f	14	34	34	43	1	F 23
5.2. 44	31.3. 44	T. R.	m	10 ½	32	32	44	1	F 17
5.2. 44	31.3. 44	A. R.	m	4	21	21	46	2	F 18
6.7. 44	20.8. 44	O. N.	m	7	21	21	47	2	F 26
18.1. 44	25.7. 44	K. N.	m	4 ½	16	16	48	3	D 22
20.2. 44	29.4. 44	B. N.	m	5	17 ½	18	58	3	D 26
14.4. 44	8.5. 44	F. C.	m	6	18 ½	19	63	3	E 9
30.4. 44	2.6. 44	I. L.	f	7	21	21	75	3 ½	D 33
12.6. 44	15.7. 44	F. J.	f	7	22	22	85	4	F 22
2.2. 44	8.2. 44	A. B.	f	12	39	39	110	3	D 21
20.8. 44	7.9. 44	E. H.	f	9	28	28	220	8	D 42

It is evident that $b < me(b)$ in the $\frac{2}{3}$ g/kg group, i.e. it cannot be proved that β differs from 0 or that the elimination increases with the quantity administered, whereas the 1 g/kg group reveals a β distinctly > 0 . *The following, therefore, only deals with the 1 g/kg group.* (The fact that β is not > 0 in the $\frac{2}{3}$ g/kg group presumably is due to the largest dosage in this group being 26 g, whereas it was 38 g in the 1 g/kg group, and the larger the dose the greater is the possibility of proving the dependence of the elimination on the dose.) It is evident that α cannot be calculated with certainty, but it does not differ essentially from 0. It was therefore investigated whether α might be $= 0$, i.e. whether the elimination might be proportional to the administered quantity (which would have the consequence that the 0-eliminations would constitute a constant percentage, about 36 per cent). Elaborate calculations, which will not be included in this report, revealed that there was nothing to prevent such a possibility.

Accepting the hypothesis as to the proportionality of the elimination to the quantity administered we find the estimate of the slope to be:

$$b = 0.725$$

and the estimate of the dispersion factor:

$$k = 2.02$$

and the mean errors of both

$$me(b) = 0.274 \quad \text{and} \quad me(k) = 0.314.$$

On this basis an upper limit for the elimination of normal subjects, placed so high that 95 per cent are situated below, was calculated as mentioned above.

Summary.

A survey of the literature on galactose tolerance tests on children is followed by a report on the writer's 100 galactose tolerance tests using 78 children with unimpaired livers, ranging in age from 2 to 14. Given a quantity of 1 gramme galactose per kilo body weight 95 per cent of children with unimpaired livers proved to eliminate a maximum of 4 per cent of the galactose administered. If the stated dosage is used, it is sufficient to examine the urine from the first 3 hours. The subject should be fasting before and during the test.

References.

1. FABISCH, W. & F. ETZOLD: *Ztschr. f. Kinderh.* 55: 702—707, 1933.
 - 2. HEYMANN, W. & I. HOWE: *Ztschr. f. Kinderh.* 53: 629—649, 1932. —
 3. HALLMANN, L.: *Klin. Chemie und Mikroskopie*. 3rd Ed. Thieme, Leipzig, p. 159 (1943). —
 4. CHOMET, B.: *Arch. f. Kinderh.* 105: 86—91, 1935. —
 5. MEYER, S. & G. STERN: *Arch. f. Kinderh.* 68: 241—254, 1921. —
 6. WEECH, A. ASHLEY in: *Holt's Dis. Infancy and Childhood*, 11th Ed. Appleton Century, London p. 469 (1939). —
 7. GEILL, T.: *Acta med. Scandinav.* 81: 31—62, 1934. —
 8. NISSEN, N. I.: *Ugeskr. f. Læger* 99: 427—437, 1937. —
 9. —: *Hospitaltid.* 80: 1197—1203, 1937. —
 10. IPSEN, J. & N. JERNE: *Acta pathol.* 21: 343—361, 1944. —
 11. HALD, A., M. JERSILD & G. RASCH: *Acta pathol.* 20: 64—85, 1943.
-

AUS DEM KINDERKRANKENHAUS DER UNIVERSITÄT HELSINKI, VORSTAND PROF. DR. ARVO YLPPÖ, UND DER HEBAMMEN-LEHRANSTALT IN HELSINKI, VORSTAND DOZ. A. APAJALAHTI.

Untersuchungen über das weisse Blutbild bei Frühgeburten im Zusammenhang mit regelmässiger Ernährung und Hunger sowie Schwankungen der Körpertemperatur.

Von

AINO YLIRUOKANEN.

Im weissen peripherischen Blutbild treten zeitweilig beträchtliche, schnell vorübergehende sowohl quantitative als auch qualitative Schwankungen auf. Man hat versucht, als Ursache dieser Schwankungen verschiedene normale physiologische Zustände zu erklären, und in diesem Sinne sind eine grosse Menge Untersuchungen über die Beziehung der Ernährung, der Schwankungen der Körpertemperatur, der Bewegung usw. zum weissen Blutbild durchgeführt worden.

Besonders bedeutend ist die Labilität des weissen Blutbildes bei Kleinkindern und vorzüglich bei Frühgeburten. Bei den jungen Frühgeburten kann kein einheitliches Schema angegeben werden. Die Gesamtanzahl der Leukozyten wechselt stark (KUNCHEL, LICHTENSTEIN, FLETCHER und MITCHELL, WASHBURN, VAN CREVELD), im allgemeinen ist sie niedriger als bei den Erwachsenen und steigt auch bei Infektionen keineswegs immer an (DE VICARIS, LANDÉ), was z. B. LANDÉ für eine Insuffizienz des »granulozytären Apparats« hält.

Im qualitativen Blutbild sind ebenfalls grosse, auch tägliche Schwankungen festgestellt worden. Im allgemeinen haben die Frühgeburten Lymphozytose (SCHMAL, SCHMIDT und SEREBRINSKIJ, SCHMID, VAN CREVELD, ARNETH). Im Vergleich zu den entsprechenden Zahlen bei ausgetragenen Kindern sind die Zellmengen sowohl hinsichtlich der Gesamtanzahl der weissen Blutzellen als auch des differenzierten Blutbilds bei den Frühgebur-

ten niedriger, was auf eine Insuffizienz des hämatopoetischen Systems hinweist (MAGNUSSON).

Der Einfluss der Nahrung auf das weisse Blutbild ist viel untersucht worden, und die sog. Verdauungsleukozytose hat die Forscher seit Jahrzehnten interessiert, und die verschiedensten Resultate sind erhalten worden. Die Ursache der Verdauungsleukozytose ist auf viele Weise z. B. als Verteilungsleukozytose erklärt worden, die auf der verschiedenen Grösse der Blutzellen, den Schwankungen der Blutkonzentration usw. beruht. Die Leukozytose ist nach einigen Forschern eine Polynukleose, nach anderen eine Lymphozytose oder sogar beide. Es gibt Forscher, die zu negativen Ergebnissen gekommen sind, das heisst also, dass eine sog. Verdauungsleukozytose überhaupt nicht gäbe.

Bei den mit Kindern ausgeführten Versuchen ist man desgleichen zu verschiedenen Resultaten gekommen. Leukozytose haben festgestellt u. a. SSOKOLOV und KONOVALOVO, MADON, Leukopenie insbesondere bei Kleinkindern GRABENSEE, FLETCHER und MITCHELL und bei diesen auch SSOKOLOV und KONOVALOVO. Zahlreiche Forscher sind dagegen zu dem Schluss gekommen, dass die Nahrung und ihre verschiedenen Arten keinen Einfluss auf das weisse Blutbild hätten (SCHMAL, SCHMIDT und SEREBRINSKI, LÖWENTHAL, GYLLENSWÄRD, WASHBURN). GYLLENSWÄRD hat die Beziehung zwischen der Digestion und dem weissen Blutbild weitläufig untersucht und dabei festgestellt, dass die gewöhnliche Ernährung keine leukozytäre Reaktion hervorruft, dass aber nach genügend langem Hungerzustand (14—16 Stunden) das weisse Blutbild sich zum sog. Hungertyp verändert, der unter dem Einfluss der Nahrung nach einer Periode von mehreren Stunden wieder zum Normaltyp wird. Dass bei den Untersuchungen diese leukozytäre Reaktion nicht beobachtet worden ist, beruht darauf, dass sie in zu kurzer Zeit ausgeführt worden sind. Im sog. Hungertyp tritt deutliche Neutrophilie sowie Eosino- und Lymphopenie auf. Die Erscheinung hängt offensichtlich nicht von der Verteilungsleukozytose ab, sondern sie geschieht durch Aufschwemmung der Zellen aus den Zellvorräten.

Auch andere physiologische Zustände sind als Urheber der leichten Schwankungen des weissen Blutbildes angeführt wor-

den. WERNSTEDT untersuchte die »motorische leukozytäre Reaktion«, und HESS und SEYDERHOLM hielten die sog. Schreileukozytose für Lymphozytose. Bei seinen an Kleinkindern ausgeführten Versuchen stellte WASHBURN fest, dass die Schwankung der weissen Blutkörperchen keinen regelmässigen Rhythmus hinsichtlich der Ernährung, der Bewegung, des Schlafs oder anderer äusseren Umstände zeigt.

Im Zusammenhang mit künstlichen Schwankungen der Körpertemperatur haben COHEN und STAFFORD bei Erwachsenen Leukozytose und relative Polynukleose beobachtet, das Maximum nach ca. 6 Stunden. DE LA GRANDA machte Untersuchungen bei 4—6-jährigen Kindern nach heissen Handbädern und erhielt als Resultat relative Lymphozytose und Mononukleose. Bei Frühgeburten machten KIJANEN und HIETARINTA Versuche mit heissen Bädern, welche z. T. Leukozytose hervorriefen, was jedoch nicht regelmässig der Fall war, und in einigen Fällen kam sogar Leukopenie vor. MAASIK untersuchte Veränderungen des weissen Blutbildes und der Anzahl der Erythrozyten bei Säuglingen im Zusammenhang mit künstlichem Fieber und stellte fast regelmässig Leukozytose und Neutrophilie fest, sowie gleichzeitig und noch leichter auftretende Verminderung der Anzahl der Erythrozyten. Die Veränderungen des weissen Blutbild waren allerdings nicht in allen Fällen ebenso beträchtlich.

Eigene Untersuchungen.

Zur Untersuchung der durch regelmässige Ernährung und Hunger erzeugten leukozytären Reaktion wurden bei 6 Frühgeburten insgesamt 15 Versuche durchgeführt, bei welchen im ganzen 132 weisse Blutbilder genommen wurden. In 6 Fällen wurde der Versuch unter Anwendung einer gewöhnlichen Mahlzeit und 24-stündigem Fasten (Wasserdiet) ausgeführt. In den meisten Fällen bestand die Mahlzeit aus Muttermilch, in 2 Fällen $\frac{1}{2}$ -Milch und in 2 Fällen $\frac{1}{1}$ -Milch. Die Blutproben wurden vom Aussenrand der Ferse genommen, abwechselnd von der rechten und linken Ferse. Die Zählungen der Gesamtanzahl der Leukozyten wurden mit der Zählkammer von Türk gemacht. Für

die Differenzierung wurden die Präparate mit der gewöhnlichen May-Grünvald-Giemsa-Methode gefärbt.

Die Versuche wurden nach folgendem Schema gemacht:

I. Untersuchungstag: 9.00 Uhr Blutbild, 10.00 Uhr Mahlzeit.

Blutbild um 10.15, 10.30, 11.00, 11.30, 12.00, 13.00, 14.00 Uhr.

II. Untersuchungstag: 8.00 Uhr Blutbild, desgleichen 9.00 und 10.00 Uhr. 10.00 Uhr Mahlzeit.

Blutbild um 10.15, 10.30, 11.00, 11.30, 12.00, 13.00, 14.00 Uhr.

Zur Zeit der gewöhnlichen Mahlzeiten wurde die entsprechende Menge Wasser verabreicht. In den Versuchen 1—10 wurde Muttermilch gegeben, 11—12 und 14 $\frac{1}{5}$ -Milch, 13 $\frac{1}{1}$ -Milch. Es wurde für unnötig gehalten, von der regelmässig verabreichten Milch oder Milchnischung abzuweichen, da zahlreiche Forscher festgestellt haben, dass die Beschaffenheit der Nahrung keine Bedeutung hat. Die Versuche wurden mit gesunden Frühgeburten ausgeführt, von welchen ein Verzeichnis beigelegt ist.

Der Klarheit wegen sind die Versuche in Tabellen dargestellt, nämlich Tabelle 1, 2 und 3, von welchen jede eine Serie von 2 Versuchen enthält (ohne Fasten und nach dem Fasten). Tabelle 1 enthält die Versuche 1—2 und 3—4. Die Versuche 1—2 sind mit ——— bezeichnet und die Versuche 3—4 mit ----- . Aus der Tabelle geht hervor, dass die Gesamtanzahl der Leukozyten bei beiden unregelmässige, von den Mahlzeiten unabhängige Schwankungen zeigt. In den Versuchen 1—2 scheinen die Lymphozyten der Gesamtleukozytenkurve zu folgen, während wiederum bezüglich der anderen Zellenarten keine deutliche Einheitlichkeit vorhanden zu sein scheint. In den Versuchen 3—4 scheinen die Neutrophilen und Lymphozyten der Gesamtleukozytenkurve zu folgen. Wenn man die verschiedenen Zellsorten gesondert betrachtet, stellt man fest, dass die Eosinophilen nach dem Fasten abgenommen haben, ja sogar fast verschwunden sind. In beiden Fällen haben die Neutrophilen nach dem Fasten deutlich zugenommen und die Lymphozyten ein wenig abgenommen. Im Versuche 2 haben die Eosinophilen von 4,5 % zu 1—0 % und die Lymphozyten von 80 % zu 60—70 % abgenommen; die Neutrophilen haben von 15 % zu 30—40 % zugenommen. Bei den Monozyten lassen sich unbestimmte Schwankungen feststellen.

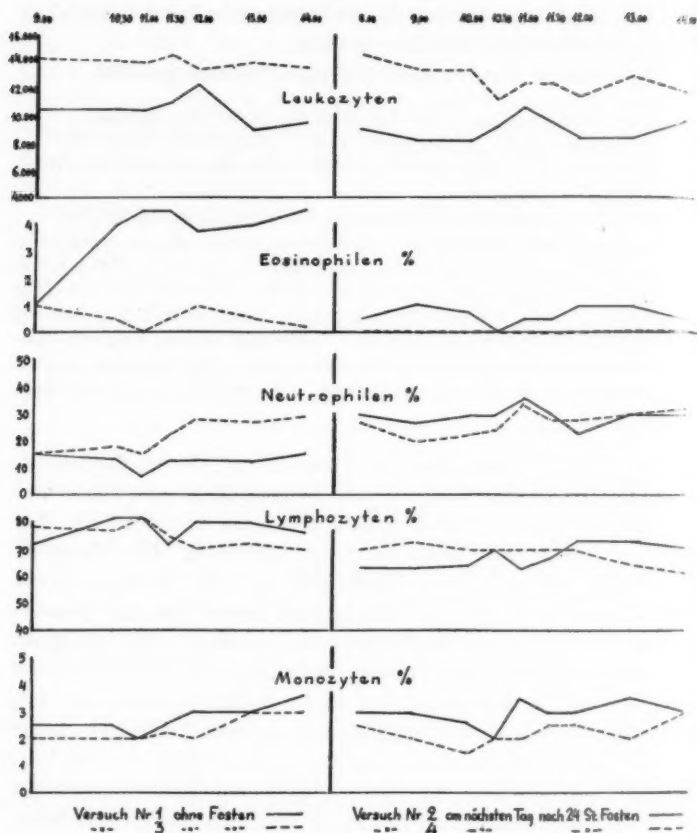


Tabelle 1.

Tabelle 2 zeigt die Kurven aus den Versuchen 5—6 und 7—8. Auch hier sind die Schwankungen der Gesamtleukozytenmengen unabhängig von den Mahlzeiten. Die Eosinophilen nahmen in beiden nach dem Fasten ab, im Versuche 6 von 2,5 % zu 0—0,5 %; im Versuche 8 von 1,5 % zu 0. Bei Versuch 6 tritt nach dem Fasten etwas Neutrophilie 10—15 % auf, bei Versuch 8 kaum nennenswert. Die Lymphozytenkurven verändern sich nicht in

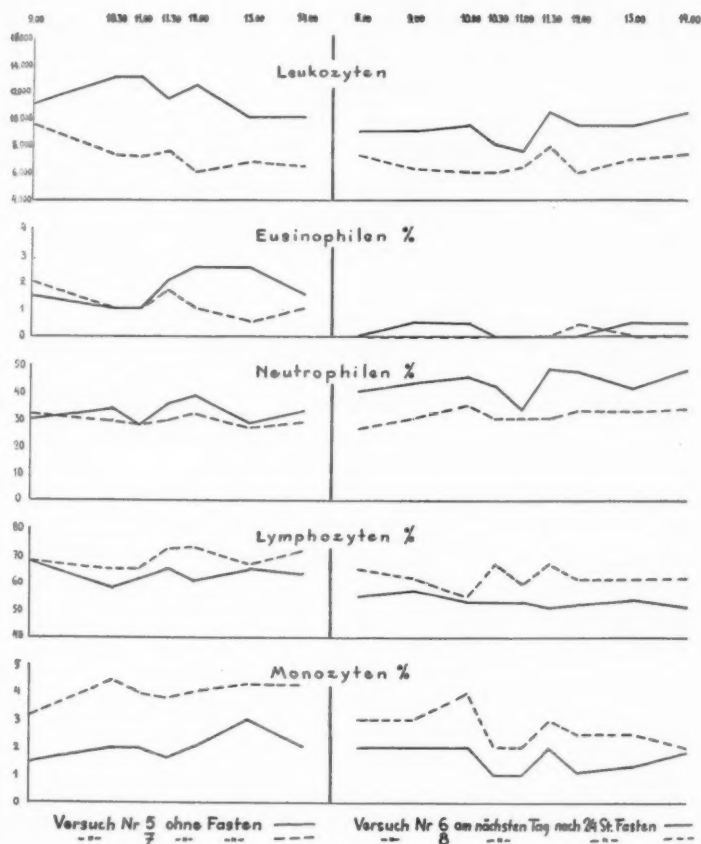


Tabelle 2.

gleichem Masse. Im Versuche 6 haben die Lymphozyten von 65 % zu 55—50 % abgenommen. Die Monozyten nahmen in Versuch 8 ab.

Tabelle 3 zeigt die Kurven der Versuche 9—10 und 11—12, in welchen ebenfalls unregelmässige Veränderungen der Gesamtleukozytenmenge zu beobachten sind. Deutliche Eosinopenie tritt in Fall 10 auf, von 1—2 % zu 0—0,5 % und im Versuch

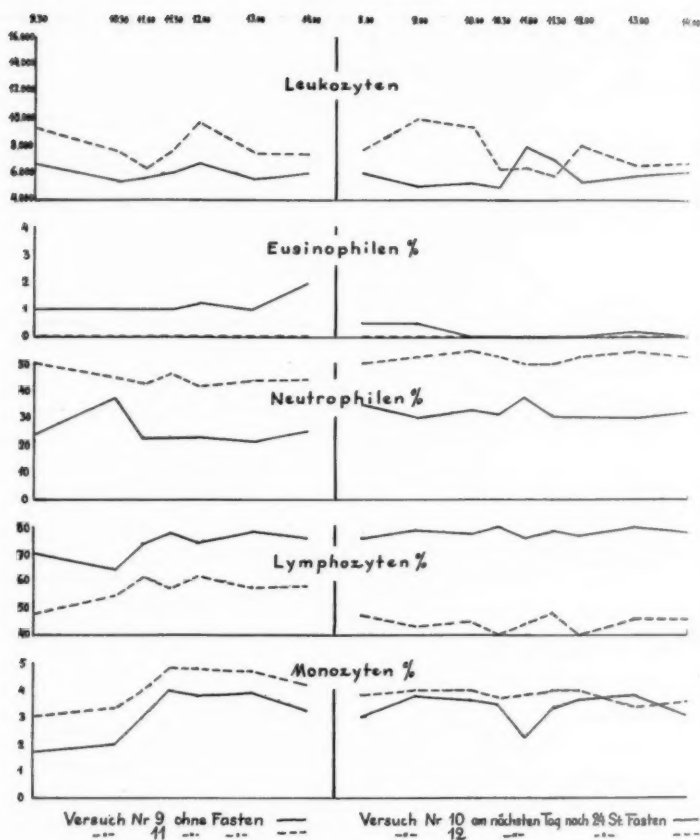


Tabelle 3.

12 beträchtliche Neutrophilie um 20 % nach der Wasserdiet. Die Monozyten zeigen unregelmässige Schwankungen. Bei Versuch 12 ist offensichtliche Lymphopenie vorhanden.

Gemeinsam für diese Versuche ist also die Unabhängigkeit der Gesamtanzahl der Leukozyten von den Mahlzeiten; nach dem Fasten deutliche Eosinopenie und Neutrophilie und meistens auch Lymphopenie. Die Monozyten zeigen keine regelmässig auftre-

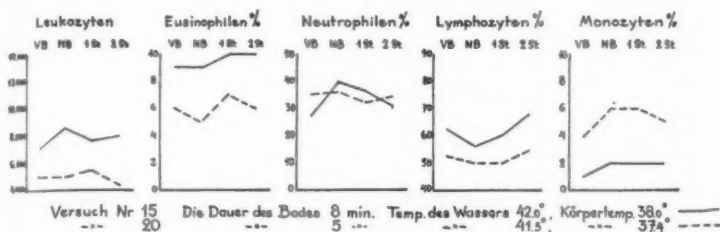


Tabelle 4.

tenden Schwankungen. 4 Stunden nach der nach dem Fasten genossenen Mahlzeit sind die Werte noch nicht auf ihr früheres Niveau zurückgekehrt.

Die Versuche 13, 14 und 15 wurden ohne Fasten ausgeführt, 13 mit $\frac{1}{2}$ -Milch, 14 mit Muttermilch und 15 mit $\frac{1}{1}$ -Milch. Im quantitativen und differenzierten Blutbild treten bei allen Fällen von den Mahlzeiten unabhängige Schwankungen auf.

Zur Untersuchung der leukozytären Reaktion im Zusammenhang mit den durch heisse Bäder erzeugten Schwankungen der Körpertemperatur wurden bei 17 Frühgeburten insgesamt 20 Versuche gemacht und 77 weisse Blutbilder genommen. Die Blutproben wurden vor dem Bad, sogleich danach, 1 Stunde und 2 Stunden danach entnommen. In der Tabelle 4 sind die Blutbilder aus den Versuchen 15 und 20, in der Tabelle 5 aus den Versuchen 6 und 12 dargestellt. Ein Verzeichnis über die Patienten ist beigelegt. Die leukozytäre Reaktion, die auf den durch heisse Bäder erzeugten Anstieg der Körpertemperatur folgte, war in den verschiedenen Fällen sehr verschieden. Leukozytose kommt in 7 Fällen vor (3, 5, 6, 15, 17, 18, 19), die höchsten Werte der Zunahme um 2 500. Bei den übrigen blieb die Leukozytenmenge ziemlich unverändert, oder es kommen unregelmässige Schwankungen vor, bei einem Teil jedoch Leukopenie um ca. 1 000 Leukozyten. Neutrophilie kommt in 9 Fällen vor, die Zunahme 10—30 % und sie folgt der Gesamtleukozytenmenge. Bei den anderen Fällen werden in der Anzahl der Neutrophilen nur geringe mit der Steigerung der Körpertemperatur verbundene Veränderungen festgestellt. Die Schwankungen der übrigen Zellgruppen sind

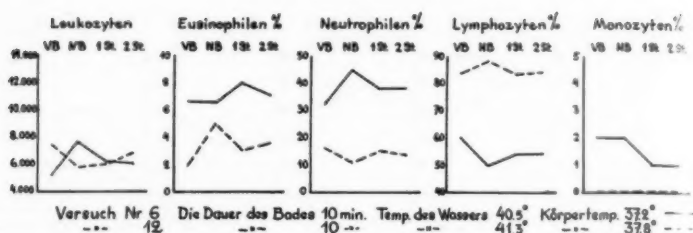


Tabelle 5.

ihrer Natur nach unbestimmt. Im allgemeinen sind die Leukozyten- ebenso wie die Neutrophilen-Werte nach 2 Stunden zu ihren Ausgangswerten zurückgekehrt.

Unter Berücksichtigung der leukozytären Reaktion und des Geburtsgewichts des Patienten, mit anderen Worten der Prä-maturität sowie des Alters war von denjenigen, welche mit Leukozytose reagiert hatten, bei dreien das Geburtsgewicht über 2 000 g, das Alter 12—21 Tage, bei 2 das Geburtsgewicht über 1 500 g und das Alter 6—24 Tage sowie bei 2 das Geburtsgewicht über 1 250 g und das Alter 7—18 Tage. Die Prä-maturität oder das Alter scheint also keine entscheidende Bedeutung zu haben. Die Körpertemperatur stieg auf 37,2—39°, was ebenfalls die Anzahl der Leukozyten nicht beeinflusst zu haben scheint. Die gleichen Beobachtungen können auch in den anderen Fällen gemacht werden. Als allgemeine Erscheinung wird schwaches Reagieren des weissen Blutbildes auf die künstlich hervorgerufenen Schwankungen der Körpertemperatur beobachtet.

Zusammenfassung.

Die leukozytäre Reaktion bei Frühgeburten wurde hinsichtlich regelmässiger Ernährung und Hunger sowie Schwankungen der Körpertemperatur untersucht. Bei regelmässiger Ernährung konnte kein Einfluss der Mahlzeiten oder der Beschaffenheit der Nahrung auf die Schwankungen des weissen Blutbildes festgestellt werden. Nach 24-stündigem Fasten (Wasserdiet) traten in der Gesamtleukozytenmenge unregelmässige Veränderungen auf. Im

Verzeichnis der Patienten.

Ernährungsversuche:

	geb.	Gg.		Gw.
1-2 Matti N.	14.11.40	2300 g,	1 $\frac{1}{2}$ Mon. Frühgb.	28.11.40 2180 g
3-4 Elina J.	13.2. 41	1850 »	2 » »	26.5. 41 2560 »
5-6 Hannu S.	1.5. 41	2200 »	Zwilling, ausgetragen	29.5. 41 1880 »
7-8 » »	»	» »	» »	9.6. 41 2180 »
9-10 Helvi S.	1.5. 41	2200 »	» »	6.6. 41 1920 »
11-12 Pertti J.	13.5. 41	1660 »	2 Mon. Frühgb.	4.6. 41 1440 »
13 » »	»	» »	» »	13.6. 41 1500 »
14 Yrjö J.	2.10.40	1800 »	» »	21.10.41 1880 »

Wärmeversuche:

	geb.	Gg.		Gw.
1 Ulla K.	1.8. 40	1950 g,	2 Mon. Frühgb.	6.8. 40 1800 g
2 Heino L.	4.8. 40	1800 »	» » »	12.8. 40 1680 »
3 Konrad B.	23.7. 40	2050 »	1 Mon. »	14.8. 40 1680 »
4 Kyllikki S.	1.5. 40	1480 »	2 Mon. »	17.8. 40 1980 »
5 Benita D.	30.7. 40	2550 »	3 Woch. »	19.8. 40 2480 »
6 Tellervo L.	4.8. 40	1450 »	2 Mon. »	22.8. 40 1680 »
7 = 1.				30.8. 40 1900 »
8 = 6.				3.9. 40 1670 »
9 = 3.				6.9. 40 2220 »
10 Knabe K.	8.9. 40	2180 »	1 Mon. »	13.9. 40 2140 »
11 Mädchen K.	14.9. 40	2470 »	3 Woch. »	16.9. 40 2360 »
12 Eila	16.9. 40	1800 »	2 Mon. »	16.9. 40 1800 »
13 Mädchen K.	2.10.40	2000 »	2 Mon. »	5.10.40 2390 »
14 Mädchen N.	3.10.40	2340 »	1 Mon. »	8.10.40 2260 »
15 Yrjö J.	21.9. 40	1900 »	2 Mon. »	16.10.40 1800 »
16 Knabe N.	16.10.40	2320 »	1 Mon. »	19.10.40 2130 »
17 Knabe P.	18.10.40	1340 »	2 Mon. »	25.10.40 1360 »
18 Kauko U.	26.10.40	2020 »	1 $\frac{1}{2}$ Mon. »	7.11.40 1880 »
19 Lahja V.	12.11.40	1680 »	1 $\frac{1}{2}$ Mon. »	Zwilling 16.11.40 1680 »
20 Irmeli V.	12.11.40	1270 »	1 $\frac{1}{2}$ Mon. »	19.11.40 1150 »

differenzierten weissen Blutbild dagegen erschienen in fast allen Fällen nach 24-stündigem Fasten beträchtliche Eosinopenie und Lymphopenie sowie ziemliche Neutrophilie. Die Schwankungen der Monozyten folgten keinem regelmässigen Rhythmus. Bei Proben, die nach einer nach dem Fasten genossenen Mahlzeit genommen wurden, waren diese Werte im Verlauf von 4 Stunden noch nicht zu ihren Ausgangswerte zurückgekehrt.

Die künstlichen Schwankungen der Körpertemperatur, die durch heisse Bäder erzeugt wurden, riefen im allgemeinen geringe Reaktionen sowohl im quantitativen als auch im qualitativen weissen Blutbild hervor. In vielen Fällen wurde etwas Leukozytose und Neutrophilie festgestellt, in anderen aber wieder Leukopenie. Die Schwankungen waren unabhängig von der Prämatunität oder dem Alter des Patienten.

Schrifttum.

- ARNETH, J., *Monschr. f. Kinderheilk.* 73, 1938, S. 115. — VAN CREVELD, S., *Monschr. Kindergeneesk.* 6, 1936 (Ref. *Am. J. of Dis. of Child.* 1937, vol. 54). — FLETCHER und MITCHELL, *Am. J. Dis. of Child.* 34, 1927. — GRABENSEE, *Leitschr. J. Kinderheilk.* 45 (H. 1—2, S. 36—44) 1927. — GYLLENSWÄRD, *Acta Ped. Scand.* vol. X, 1930. — DE LA GRANDA und VEGAS, *Refer. Zbl. für Kinderheilk.* 1937, S. 581. — HERZ, *Monatschr. Kinderheilk.* 40, 1928. — KUNCKEL, *Zeitschr. Kinderheilk.* XIII, 1916. — LANDÉ, *Zeitschr. Kinderheilk.* XXII, 1919. — LICHTENSTEIN, *Sv. Läkarsällsk. handl.* 43, 1533, 1917. — LÖWENTHAL, *Deutsche med. Wochenschr.* 53, 1927. — MAASIK, E., *Acta Paediatr.* XXXII, 1945. — MADON, *Zbl. Kinderheilk.* 1930 (Referat). — MAGNUSSON, *Acta Ped. Scand.* XXIII, 1939. — SCHMAL, SCHMIDT und SEREBRINSKIJ, *Zeitschr. Kinderheilk.* XLI, 1926. — SCHMID, *Monatschr. Kinderheilk.* XXIX, 1925. — SOKOLOV und KONOVALOVO, *Zbl. Kinderheilk.* 1926 (Referat). — COHEN und STAFFORD, *J. clin. Inv.* 194, 1935, Referat *Kongress-Zbl.* 82, 1935. — WALTER, *Zbl. Kinderheilk.* 21, 1928. — WASHBURN, *Am. J. of Dis. of Child.* 47, 1934. — WERNSTEDT, *Fol. haematol.* 12, II, 173, 1912.
-

Propriozeptiver Reflex und Willenshandlung.

Von

DAVID KATZ und THEODOR KÜNNAPAS.

Die folgenden Untersuchungen stellen einen Beitrag zur Frage nach den Beziehungen zwischen propriozeptiven Reflexen und Willenshandlungen dar. Es gilt einige neue Gesichtspunkte gegenüber diesem Problem geltend zu machen, dem nicht so viel Beachtung von psychologischer Seite geschenkt worden ist, wie es unseres Erachtens verdiente. Im Zusammenhang mit Experimenten über die elastischen Eigenschaften von Brotteig, die Katz im Auftrag der Research Association of British Flour Millers ausgeführt hat, ist er auf die Bedeutung dieser Reflexe für gewisse Leistungen der menschlichen Hand aufmerksam geworden. »If one opens the hand and moves the fingers quickly against or towards each other they will show a short opposite movement independent of our will... Let us suppose that the movement of our fingers is not made against empty space but against dough which is brought between the fingers. In a case like that an elastic dough will help the reflex movement whereas a dough of poor elasticity will hamper it. For this reason an elastic dough will give the impression of being full of life whereas a dough of poor elasticity will appear dead.«¹ Die Reflexbewegungen der Finger, von denen hier die Rede ist, sind propriozeptiver Natur im Sinne Sherringtons.² Die Innervation eines bewegten Muskels ist verknüpft mit der intrazentralen Hemmung seines Antagonisten, aber dieser Hemmung folgt unmittelbar eine intracentrale Erregung, welche eine Kontraktion des eben erschlaft gewesenen Antagonisten bewirkt. Sherrington bezeichnet diesen

¹ David Katz, Studies on test baking. III. The human factor in test baking. A psychological study. Cereal Chemistry. Vol. XIV, 1937.

² Sherrington, The integrative action of the nervous system. London 1908.

Prozess auch als »sekundäre Induktion«. Schon vor Sherrington war der Vorgang den Physiologen als Rückstossphänomen bekannt, ohne dass man eine befriedigende Erklärung dafür hätte geben können.³

Auch bei dem sogenannten Klopfest, der darin besteht, dass man jemand mit dem Finger entweder in dem persönlich angemessenen Tempo oder aber so schnell wie möglich Klopfbewegungen ausführen lässt, spielen propriozeptive Reflexbewegungen eine sehr wesentliche Rolle, eine um so grössere, je flotter das Klopftempo gewählt wird. Bei schnellsten Klopfbewegungen kann man konstatieren, dass man dabei durchaus nicht jede einzelne Fingerbewegung wollen muss. Vielmehr verhält es sich damit so, dass die Absicht 'so schnell als möglich' zur Folge hat, dass der Finger sich in Gang setzt und in Gang bleibt, bis man nicht mehr will. »Durch seinen Vorsatz hat man einen Apparat in Gang gebracht, der seine eigne Gesetzmässigkeit hat und in dessen verschiedene Bewegungsphasen man nicht einzugreifen braucht.«⁴ Nicht wenige Versuchspersonen kommen bis auf 7 Klopfbewegungen in der Sekunde, und man kann natürlich nicht annehmen, dass dies eine Folge davon ist, dass man in der Sekunde siebenmal will. Gegen die Willkürlichkeit des Bewegungsablaufs spricht auch der Umstand, dass man sich ohne Schwierigkeit während des Ausführung der Bewegungen mit ganz anderen Sachen beschäftigen, sich z. B. unterhalten kann, vorausgesetzt nur, dass im Hintergrund des Bewusstseins der Befehl an den Bewegungsapparat aufrechterhalten wird. Noch deutlicher spricht gegen die Annahme, man wolle jede Phase der Klopfbewegungen, die Tatsache, dass man bei Ausführung der Klopfbewegungen links und rechts gleichzeitig auf beiden Seiten etwas verschiedene

³ Für die Orientierung über die Geschichte unseres Problems verweisen wir auf:

1. Rieger, Untersuchungen über Muskelstände. Jena 1906.
2. M. Isserlin, Über den Ablauf einfacher willkürlicher Bewegungen. Psychologische Arbeiten, Bd. 6, 1914.
3. K. Wachholder, Beiträge zur Physiologie der willkürlichen Bewegung. Pflügers Archiv für die gesamte Physiologie. Bd. 209, 1925.

⁴ David Katz, Nya psykologiska strövtåg. (Neue psychologische Streifzüge.) Stockholm 1945.

Werte erhält — bei einem Rechtshänder rechts etwa 6 und links 5 — und es wäre doch ungereimt anzunehmen, jemand könne gleichzeitig rechts sechsmal und links fünfmal in der Sekunde wollen.

Die hier mitgeteilten Beobachtungen vertragen sich nicht mit der sog. Aufmerksamkeits-theorie der willkürlichen Bewegung »nach der die Ausführung einer auf ein bestimmtes Ziel gerichteten Handlung, für die man sich entschieden hat, dadurch zustandekomme, dass die Entscheidung für dieselbe eine Betonung der betreffenden Zielvorstellung durch die Aufmerksamkeit und eine Befreiung derselben von den hemmenden Wirkungen anderen Zielvorstellungen und etwaiger sonstiger Erwägungen einschliesse».⁵ Hierdurch erlange die Zielvorstellung die Kraft, die ihr entsprechende Bewegung wirklich ins Leben zu rufen. Unsere Beobachtungen vertragen sich viel besser mit der von G. E. Müller entwickelten Impulstheorie der willkürlichen Bewegung. Sie hat folgenden Inhalt. »Gewisse willkürliche Bewegungen kommen dadurch zustande, dass auftretende Ziel- oder Bewegungsvorstellungen in zentralen Teilen der motorischen Bahnen, welche die ihnen entsprechenden motorischen Erregungen zu durchlaufen haben, einen Zustand erhöhter Reizbarkeit schaffen, und dass hierauf ein motorischer Willensimpuls folgt, dem ein physiologischer Erregungsantrieb entspricht. Das Hinzukommen dieses Erregungsantriebs zu jener ideomotorischen Bahnung hat das Eintreten der Bewegung zur Folge.»

Man kann die oben beschriebenen Klopfbewegungen sicher als gewollte bezeichnen, aber nicht in dem Sinn, dass sie in jeder einzelnen Bewegungsphase dem Willen unterworfen wären, von ihm beherrscht würden. Wir wollen den Begriff »beherrschte Bewegung» für den Fall reservieren, dass selbst der kleinste Teil der Bewegung genau so ausgeführt wird, wie man ihn haben will. Das Kopieren einer aus kleinsten Elementen bestehenden und nach Winkeln und Bruchstückgrößen dauernd variierenden Zickzacklinie fordert zu einer maximal beherrschten Bewegung heraus. Eine beherrschte Bewegung kann niemals schnell ausge-

⁵ G. E. Müller, Zur Theorie der willkürlichen Bewegung. Bericht über den 8. Kongress für experimentelle Psychologie. Jena 1924.

führt werden. Je grösser die Forderungen sind, die an eine Bewegung hinsichtlich ihrer Elemente gestellt werden, um so mehr entfernt sie sich von dem Typus der propriozeptiven Reflexbewegung.

Am meisten maschinenartigen Charakter haben hin- und hergehende Bewegungen, wie z. B. Klopfbewegungen maximaler Geschwindigkeit. Sie haben auch die grösste Regelmässigkeit. Geht man zu einem etwas langsameren Tempo über, so bleibt zwar auch dann noch die Regelmässigkeit sehr gross, aber sie ist doch nicht so gross wie bei maximaler Schnelligkeit. Auch traut man es sich dann nicht mehr ohne weiteres zu, während des Schlagens die Aufmerksamkeit andern Dingen zuzuwenden. Was vollends eine ganz unerfüllbare Aufgabe wird, das ist, mit der rechten Hand das eine und mit der linken ein etwas davon abweichendes Tempo genau einzuhalten, sofern dieses nicht mehr das schnellste ist.

Man kann ohne Übertreibung sagen, dass es keine einzige mit einer gewissen Geschwindigkeit ausgeführte Bewegung einer Gliedmasse gibt, die ohne Rückstoss bleibt. Um einen Spezialfall herauszuheben, so hat bereits Rieger auf dessen Bedeutung bei den Schreibbewegungen aufmerksam gemacht. Wie sehr der Rückstoss in unsere Willkürbewegungen eingreift, das kommt trefflich in einer Formulierung Isserlins zum Ausdruck: »Die Intention bei den Willkürbewegungen berücksichtigt den Rückstoss dauernd, indem sie ihn verwertet, vermeidet, abbremst, oder unbeeinflusst verlaufen lässt.« Nicht weniger greift der Rückstoss in automatisch gewordene Bewegungen in, deren Schnelligkeit oberhalb einer gewissen Grenze liegt. Eine eingehende Untersuchung des Rückstosses hat Wachholder zu der Auffassung geführt, dass nicht die einfache Einzelbewegung als die elementarste angesehen werden kann, aus der sich die andern zusammensetzen. »Es muss vielmehr die Hin- und Herbewegung als die elementare Tätigkeitsform des physiologischen Bewegungsmechanismus betrachtet werden, die Einzelbewegung dagegen, einerlei ob willkürlich oder reflektorisch ausgelöst, als eine komplizierte sekundäre Modifikation der ursprünglichen rhythmischen Funktionsart.... So gesehen ist die Durchführung der ein-

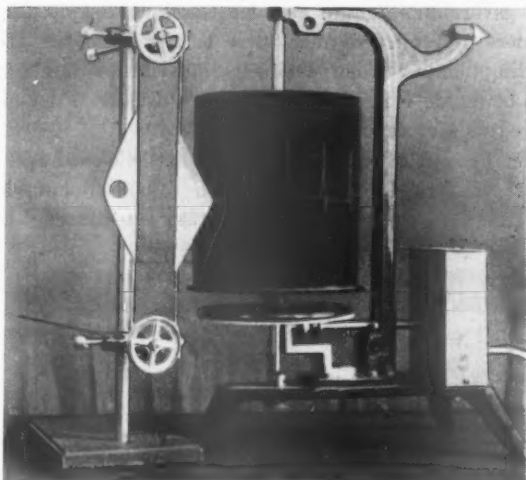


Bild 1.

fachsten arhythmischen Einzelbewegung gar nicht die elementarste Bewegungsaufgabe, ... sondern etwas höchst Kompliziertes, indem hier der Wille dem physiologischen Bewegungsmechanismus eine ihm von sich aus ganz fremde Reaktionsweise aufzwingt.»

Es sollen im folgenden einige Details des Rückstosspänomens an dem Fall der einfachen Bewegung eines Fingers (Zeigefingers) klar gemacht werden. Teils decken sich die Beobachtungsbedingungen mit solchen, denen auch andere Forscher Beachtung geschenkt haben, teils gehen sie über diese hinaus.

Die Versuchsanordnung war denkbar einfach (Bild 1). Über zwei mit Rillen versehene über einander liegende Rädchen wird eine Schnur gelegt. In diese Schnur werden zwei Kartons eingeknotet, der eine mit einer Öffnung, in die ein Finger hineinpasst, der andere mit einer Spitze versehen, um die Bewegungen des Fingers auf das berusste Papier eines Kymographions zu übertragen. Die aufgezeichneten Kurven geben die Winkelbewegungen des Fingers zwar nicht völlig korrekt, aber doch für unsere Zwecke hinreichend genau wieder. Der zeitliche Verlauf des

Bewegungsvorgangs konnte aus der Geschwindigkeit des bewegten Papiers berechnet werden, diese betrug 2 cm/sek. Die Versuchsbedingungen wurden einerseits hinsichtlich der Ausgangslage des bewegten Fingers, andererseits hinsichtlich der geforderten Bewegungsart variiert.

1. Der Finger befindet sich in einer natürlichen Lage, d. h. er ist leicht gebeugt. Die Versuchsperson (Vp) soll auf ein Kommando eine lose schnelle Beugebewegung ausführen. Die gra-

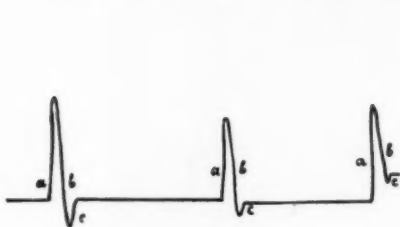


Bild 2.

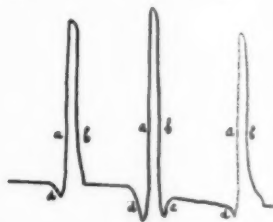


Bild 3.

phische Aufnahme (Bild 2) zeigt, dass sich an die willkürlich ausgelöste Beugebewegung (a) unmittelbar eine Streckbewegung (b), der Rückstoss, anschliesst. Wie man sieht, schnellst der Finger in manchen Fällen nicht nur in die Ausgangslage zurück, sondern sogar ein Stück darüber hinaus. An den Rückstoss schliesst sich meist, aber nicht immer, ein zweiter solcher (c) an, und vermutlich folgen hierauf noch einige weitere schwächer werdende Oszillationen, die aber mit unserer Technik nicht mehr exakt aufgefangen werden konnten. Man versteht leicht, dass unter dem Vorsatz einer fortgesetzten Bewegung aus c ohne weiteres eine neue Beugebewegung a entwickelt werden könnte.

Was das Verhältnis zwischen a und b betrifft, so liegt es bei den meisten Vpen in der Nähe von 1, manchmal ist es etwas grösser, manchmal etwas kleiner. Bei manchen Vpen tritt neben a, b und c noch eine vierte Bewegung d auf (Bild 3). Diese Bewegung ist auch von andern Experimentatoren beobachtet worden und im Sinne einer nach dem Kommando erfolgenden Vorschlagsbewegung gedeutet worden, die eine kräftigere Beugebewegung ermöglichen soll. Gewollt ist nur Bewegung a, die reflektorische

Bewegung b kommt als solche zum Bewusstsein, nicht dagegen kommen zum Bewusstsein die Bewegungen c und d.

Unsere graphischen Aufnahmen erlauben auch eine näherungsweise Berechnung der Zeiten für die einzelnen Phasen der Bewegung sowie der Geschwindigkeiten, mit denen der Finger bewegt wird. Für den Fall, der in Bild 2 festgehalten ist, wird die Bewegung a durchschnittlich in 0,07 sek. vollzogen, die Bewegung b in 0,13 sek. Die Durchschnittsgeschwindigkeit der Bewegung a beträgt 69 cm, der Bewegung b 35 cm.

2. Der Finger macht von der Ruhelage aus eine Streckbewegung. Auch an die Streckbewegung schliesst sich immer ein Rückstoss an, und dieser scheint in der Regel ausgiebiger zu sein als bei der Beugebewegung als Initialbewegung. Die Streckbewegung wird in 0,09 sek. vollzogen, der zugehörige Rückstoss in 0,12 sek. Die Differenz der Zeiten für die Ausführung einer Beuge- und einer Streckbewegung ist klein, deutet aber doch auf die auch subjektiv feststellbare Tatsache, dass es leichter ist eine Beugebewegung als eine Streckbewegung auszuführen. Aus einem Vergleich der in Versuch 1 und Versuch 2 erhaltenen Zeiten lässt sich noch ein beachtlicher Schlusssatz ziehen. Eine Beugebewegung des Fingers wird schneller ausgeführt, wenn sie gewollt wird, als wenn sie durch Rückstoss zustandekommt und dasselbe gilt für eine Streckbewegung. Hieraus kann man schliessen, dass eine Doppelbewegung mit intendierter Hin- und Herbewegung, gleichgültig ob sie mit einer Beuge- oder einer Streckbewegung beginnt, schneller ausgeführt wird als eine Bewegung in der einen oder andern Richtung mit sich anschliessendem Rückstoss. Die Doppelbewegung nimmt hierbei den Rückstoss in Gebrauch, indem sie ihn »überinnerviert«. Isserlin hat zuerst in diesem Sinne von Überinnervierung gesprochen. Über die Ausführung einer intendierten Doppelbewegung berichtet Versuch 4.

3. Der Finger wird extrem nach oben gebogen und führt von dieser Lage aus eine Beugebewegung aus. Auch hier bleibt der Rückstoss nie aus. Dieser Fall verdient ein besonderes Interesse. Eine extreme Beugung nach oben ist nämlich nur mit Mühe aufrechtzuerhalten, und bei einem Nachlassen der Anstrengung geht der Finger sofort in eine bequemere Beugelage über. Wenn sich

nun trotzdem der Rückstoss auch hier geltend macht, so versagt für dessen Erklärung vollständig die zuweilen (z. B. von Rieger) vertretene Ansicht, man habe es beim Rückstoss mit einem Vorgang zu tun, der sich aus den elastischen Eigenschaften der Muskeln oder Sehnen ergäbe.

4. Wie gestaltet sich der Bewegungsablauf, wenn die Vp dahin instruiert wird, den Finger zu beugen *und* zu strecken und nicht, wie bisher, entweder eine Beuge- oder eine Streckbewegung auszuführen? Der neue Versuch wird in zwei Variationen durchgeführt und zwar einmal so (Fall 1), dass der Finger so wie bisher schnell, ein anderesmal (Fall 2) so, dass er wesentlich langsamer bewegt wird.

Fall 1. Die Streckung wird nun, man kann sagen ausnahmslos, grösser als die Beugung. Ausserdem fällt die Bewegung c fast ausnahmslos fort, und wo sie doch auftritt, wird sie minimal. Beides spricht dafür, dass wir es hier mit einem ganz andern Bewegungstyp zu tun haben als bei den bisherigen Versuchen. Auch für das Erleben sind ja die Vorgänge von völlig verschiedener Natur. Will man nur eine Beugebewegung, so fühlt man sich auch nur für diese als Urheber, die reflektorisch sich anschliessende Bewegung kommt zwar zum Bewusstsein, aber nur wie eine Bewegung, die sich passiv an unserem Finger vollzieht. Ganz anders, wenn man eine Doppelbewegung will. Diese erlebt man als eine einheitliche, in einem Zug vollzogene und gänzlich vom Willen getragene Handlung, mit der Betonung am Schluss. Man bemüht sich, die Handlung am Schluss abzubremsen, und das hat zur Folge, dass der Finger wirklich in der extremen Streckstellung, die er erreicht, festgehalten wird. Darum fällt auch die Bewegung c so gut wie immer aus. Ich möchte noch bemerken, dass ein Aussenstehender der Doppelbewegung durchaus nicht ansehen kann, ob sie dem Typus »gewollte Beugebewegung-reflektorische Streckbewegung« oder dem Typus »gewollte Beugebewegung-gewollte Streckbewegung« angehört, erlebnismässig sind sie dagegen völlig verschieden. Man sieht, wie bereits in einem so trivialen Fall die rein behavioristische Betrachtungsweise versagt.

Fall 2. Wird die Doppelbewegung langsam ausgeführt, so

stimmen die Elongationen für Beuge- und Streckbewegung erstaunlich genau überein, häufig bis auf den Millimeter. Eine langsame Doppelbewegung ist nicht nur wie eine schnelle ganz vom Willen getragen, sondern sie ist auch so gut wie ganz vom Willen beherrscht. Jedenfalls erlebt man die Bewegung so, dass sie nicht einen Augenblick dem Eingriff des Willens entzogen ist.

5. Kann man den Rückstoss unterdrücken? Stellt man eine V_p vor diese Aufgabe, die ihr irgendwie gekünstelt erscheint, so kommt sie sozusagen »instinktiv« darauf, die Beugebewegung resp. Streckbewegung langsam auszuführen. Es sieht so aus, als ob Verlangsamung der willkürlichen Bewegung ein und zwar ein indirektes Mittel sei, um den Rückstoss zu unterdrücken. Es scheint dagegen kein direktes Verfahren für die Unterdrückung des Rückstosses zu geben. Ein anderes Verfahren den Rückstoss zu unterdrücken besteht darin, dass man die Bewegung nicht in loser, sondern in versteifter Form ausführt und den Finger extrem beugt oder streckt. Der Finger erreicht in beiden Fällen eine gewisse Endlage und wird in ihr willkürlich festhalten, über den Zeitpunkt hinaus, wo die sekundäre Induktion einzusetzen pflegt. Was das erste Verfahren angeht, den Rückstoss zu unterdrücken, so ist es recht schwer, gerade diejenige Geschwindigkeit zu treffen, bei der er ausbleibt. Wir haben die Grenze dadurch festzustellen versucht, dass wir eine Anzahl V_p en eine sehr grosse Anzahl Bewegungen haben ausführen lassen und ermittelt haben, von welchen Bewegungsgeschwindigkeiten an der Rückstoss immer ausbleibt. Bei einer V_p ., die eine maximale durchschnittliche Bewegungsgeschwindigkeit des Fingers von 118 cm/sek. erreichte, verschwand der Rückstoss bei einer Geschwindigkeit von 53 cm/sek., bei einer andern mit maximaler Geschwindigkeit von 126 cm/sek. bei 44 cm/sek., bei einer dritten schliesslich mit 96 cm/sek. bei 44 cm/sek. Man kann also sagen, der Rückstoss verschwindet, wenn die Bewegungsgeschwindigkeit des Fingers auf $\frac{1}{3}$ bis $\frac{1}{2}$ herabgesetzt wird. Ein gewisses Tempo der Prozesse im bewegten Muskel ist also Voraussetzung für den Eintritt der sekundären Induktion, unterhalb einer gewissen Geschwindigkeit fällt sie aus und nur durch ihre Modifikation gewinnen wir Einfluss auf den Rückstoss.

Es wurde in der Einleitung auf eine Erfahrung hingewiesen, die im Zusammenhang mit der Untersuchung der elastischen Eigenschaften von Brotteig gemacht wurde. Immer wenn wir einen elastischen Gegenstand mit den Fingern einer Hand umschliessen, scheint deren Rückstoss dazu beizutragen, die Elastizität des Gegenstandes deutlicher zu machen. Aber auch wenn wir einen unelastischen Gegenstand umfassen, scheint sich der Rückstoss in einer momentanen Lockerung des Griffes geltend zu machen. Dieser Frage sollen weitere Versuche gewidmet werden.

6. Die Vp erhält die Aufgabe, eine grössere Anzahl Beuge- und Streckbewegungen so schnell wie möglich hintereinander auszuführen, und zwar einmal mit dem Zeigefinger der rechten, ein anderesmal mit dem der linken Hand. Man erhält auffällig verschiedene Werte, je nachdem ob die Vp bei diesem Versuch dahin instruiert wird, die Bewegungen so auszuführen, dass jedesmal die Beugebewegung (Fall 1) oder dass die Streckbewegung (Fall 2) betont wird. Über die mit Rechtshändern erhaltenen Resultate gibt folgende Tabelle Auskunft. Die Zahlen bedeuten die Anzahl von Doppelbewegungen (Beuge-Streckbewegung) in der Sekunde.

	Fall 1		Fall 2	
	Rechts	Links	Rechts	Links
Vp. 1	6.8	6.0	3.0	2.8
Vp. 2	6.0	5.0	4.0	2.4
Vp. 3	5.7	—	3.6	—
	Am 6.2	5.5	3.5	2.6

Fall 1. Der Durchschnittswert von 6,2 für den rechten Zeigefinger stimmt recht gut überein mit dem Wert, den man erhält, wenn man annimmt, dass wir es mit einer Serie aufeinanderfolgender Bewegungen wie in Versuch 1 resp. Versuch 2 mit Ausnutzung des Rückstosses zu tun haben. In Versuch 1 erhielten wir für die Beugebewegung eine durchschnittliche Zeit von 0,07

sek., in Versuch 2 für die Streckbewegung eine solche von 0,00 sek. Zusammen ergibt das 0,16 sek. Bei Aneinanderreihung einer so zusammengesetzten Doppelbewegung kommen wir auf etwas mehr als 6 Bewegungen in der Sekunde und das ist gerade der Wert, auf den wir in der obigen Tabelle stossen. Für den linken Zeigefinger ergeben sich etwas kleinere Werte. Vielleicht darf man hieraus schliessen, dass Sherringtons sekundäre Induktion auf der linken Seite einen andern Verlauf hat als auf der rechten. — Sehr merkwürdig ist, dass für Fall 2 die Werte so viel niedriger ausfallen als für Fall 1, und zwar erhält man ungefähr nur halb so viel Bewegungen in der Sekunde wie in Fall 1. Es ist für die Selbstbeobachtung ganz auffällig, wie schwer sich schnell hintereinander Doppelbewegungen mit Betonung der Streckbewegungen ausführen lassen. Die Zeit für eine Doppelbewegung beträgt nach Versuch 2 0,21 sek., hiernach könnte man nahezu 5 Doppelbewegungen für die Sekunde erwarten aber nicht die 3,5 aus der obigen Tabelle. Es ist nicht ganz einfach zu erklären, warum die Aufgabe so schwer zu erfüllen ist, schnellste Doppelbewegungen mit Betonung der Streckbewegung auszuführen.

7. Es werden zwei Gummibänder mit einem gegenseitigen Abstand von etwa 6 cm zwischen zwei Leisten ausgespannt und die Vp. erhält die Aufgabe, einen Finger so schnell wie möglich und auf solche Weise zwischen diesen beiden Bändern zu bewegen, dass sie gerade mit ihnen in Berührung kommt, es soll aber durchaus vermieden werden, dass die Gummibänder bewegt werden. Die Folge dieser Instruktion ist, dass die Vp die Bewegungen sehr vorsichtig und damit sehr langsam ausführt. Bewegungen, die zugleich sehr schnell und sehr präcis sind, so etwas lässt sich nicht verwirklichen. Da nun die Genauigkeit an erster Stelle gefordert wird, so wird ihr die Schnelligkeit geopfert. Tatsächlich führt die Vp nur eine einzige Bewegung in der Sekunde zwischen den beiden Gummibändern aus, im Gegensatz zu den 7—8, die mit der hier bestehenden Elongation bei schnellster Bewegung möglich wären. Die Bewegung zwischen den Gummibändern ist in dem von uns definierten Sinne völlig beherrscht.

8. Während alle bisher beschriebenen Versuche mit dem Zeigefinger gemacht worden sind, wurde ein letzter mit dem Unterarm

durchgeführt. Auch bei ihm ist der Rückstoss deutlich, wenn er auch im Verhältnis zu der auslösenden Bewegung nicht so gross ausfällt wie bei der Bewegung des Fingers. Möglicherweise hängt dies damit zusammen, dass der Rückstoss zu einem wesentlichen Teil von der beträchtlichen lebendigen Kraft absorbiert wird, die bei der Bewegung des Unterarms entsteht.

Man vermisst in der Litteratur, die dem Rückstoss-Problem gewidmet worden ist, die eigentlich nahelegende genetische Fragestellung. Wie steht es mit dieser Reflexbewegung bei Kindern, unterliegt sie auch einem Reifungsvorgang und wie lernt das Kind von ihr Gebrauch zu machen? Wie lernt es das Kind — um mit Wachholder zu sprechen — seinem physiologischen Bewegungsmechanismus die ihm fremde Reaktionsweise aufzuzwingen? Dieses Problem soll bei der Fortführung unserer Versuche in Angriff genommen werden.

The incidence of rickets and tetany as a function of the variation of sunlight.

By

PAUL HORSTMANN and HELGE PETERSEN.

Rickets and tetany are very pronounced seasonal diseases, and are especially often met with during the months of winter and spring. The exact time for their culmination usually is only vaguely indicated by using such terms as: »between January and April», »between Christmas and Easter». On the other hand OSLEER (4) mentions, that rickets has its maximum in March, and GUILD (2) gives a graphic illustration of the incidence of tetany, showing a decided maximum in March and minimum in July—September. A similar curve has been published by MORO (quot. TH. MADSEN) (3).

In order to review the seasonal distribution of these two diseases in Denmark (Copenhagen), we have made a record of the date of admission to The Childrens Hospital, Fuglebakken, of all patients with these two diseases during the twelve years from 1924 to 1935.¹ All cases are recorded, whether the diagnosis of rickets or of tetany has been primary or secondary in the clinical picture. The majority of the children with tetany also had rickets. After 1936 the two diseases have decreased considerably in Copenhagen, for which reason the subsequent years have been omitted from the investigation.

A total of 1259 cases of rickets and 478 of tetany have been recorded. On the table the cases are grouped according to the

¹ We are indebted to Chief Physician VALDEMAR POULSEN, M. D., for permission to use the records of the hospital.

month of hospitalization. Chart 2 shows the seasonal distribution graphically.

The rickets curve shows its maximum in February, March and April, with nearly equal values for these three months, and has a pronounced minimum in September, while the curve of tetany has a pointed peak in March and minimum in July—October. Generally spoken, the curves of rickets and tetany show a nearly parallel course.

It is at present generally believed, that rickets and tetany are caused by lack of adequate sunlight. PALM seems to have been the first to recognize this etiological connexion. It is, however, not until after 1920 that this point of view is generally adopted in medical literature, following the understanding of the effect of light through the researches on Vitamin D. (HULDSCHINSKY 1919). For further references see: COBLENTZ (1) and SHOHL (6).

Apparently the seasonal distribution does not corroborate this view of rickets and tetany as being dependent on sunlight, the two diseases having their maximum and minimum around the equinox of the spring and of the autumn respectively, at which times the amount of sunlight received is the same, whereas the incidences do not differ very much at summer- and winter-solstices, which represent maximum and minimum respectively of direct sunlight. As on the other hand the importance of sunlight with regard to this particular disease is indisputable, the discrepancy is generally regarded as a sort of »lag», though the phenomenon has not been very much commented in literature.

Now the effect of sunlight may be supposed to increase with the length of the day, which approximately can be assumed to follow a sinus curve, $h + a \sin x$, where h is the length of the day at equinox, 12 hours, a is the amplitude of the annual variation of the length of the day, in the latitude of Copenhagen (ca. 56°) about 5 hours, and x is the time, counted from the equinox of the spring.

But in addition hereto, the intensity of sunlight depends on the declination of the sun. This variation of the intensity of the sunlight can with some approximation be expressed by $I + b \sin x$,

where, in the latitude mentioned, b is app. $= \frac{1}{3} I$.

Hence the equation

$$V = (I + b \sin x) (h + a \sin x)$$

(*I*) expresses how the effect of direct sunlight, *V*, varies with time. This curve has its maximum at summer solstice, minimum at winter solstice and equal values at the two equinoxes.

If the result of the process, brought about by the sunlight, accumulates from day to day in the body, besides being subject to continued transformation or disintegration, the effect produced will be the net yield of the positive process, viz. the accumulation, and the negative process, viz. the disintegration. Thus the state existing in any given moment does not necessarily follow the intensity of the sunlight, but depends on the variation of the radiation of sunlight as well as on the variation of the negative process. This process can in the simplest way be regarded as running steadily day and night, like other chemical processes of disintegration, which continue as long as there still remains substance to be disintegrated.

Let *k* be the result of the disintegration during twenty-four hours. The net yield of the two opposite directed processes is then

$$(I + b \sin x) (h + a \sin x) - k.^1$$

After accumulation during δx days, the net yield will be

$$(I + b \sin x) (h + a \sin x) \delta x - k \delta x$$

Integration of this expression gives the effect, *S*, accumulated from the time 0 (equinox of the spring) to the time *x*:

$$S = \left(I h + b \frac{a}{2} - k \right) x + (I a + b h) (1 - \cos x) - b \frac{a}{2} \sin x \cos x.$$

¹ This expression is based upon the assumption, that the negative process is a constant one. If it be a question of a disintegration in the common chemical sense, the negative effect will be proportional to the substance available for disintegration at a given moment, and not constant. Thereby the expression becomes more complicated, but will in all essentials yield the same result.

The value of k , the disintegration, is not known beforehand. The most reasonable presumption is that the positive and negative effects just counterbalance one another during a whole year. This means, that the expression for S becomes zero, when the accumulation is continued during one year and x consequently equals 2π .

This gives

$$k = I h + b \frac{a}{2}$$

and consequently

$$S = (I a + b h) (1 - \cos x) - b \frac{a}{2} \sin x \cos x.$$

As a is about 5 hours, $h = 12$ hours and $b = \frac{1}{3} I$, the following equation results

$$S = \frac{5}{6} I (10.8 (1 - \cos x) - \sin x \cos x) \quad (\text{II})$$

On chart 1 curve I shows the variation of the effect of direct sunlight in the course of a year, according to equation I. Curve II shows the variation of the net yield of the positive, accumulated effect of sunlight and the continuous negative, disintegrating effect in the body (equation II). From these curves it is noted, that in the latter case the maximum yield of the irradiation of sunlight does not take place until the equinox of the autumn, while the minimum yield is found at the equinox of the spring.

From this may be deducted, that potential biological effects of sunlight — having the characteristic, that they accumulate in the course of time and that the change produced disappears in the course of time — must result in an annual variation, showing maximum around the equinox of the autumn and minimum around the equinox of the spring (September and March respectively on the northern hemisphere).

This gives us the possibility to understand the above mentioned «lag» of the maximum incidence of rickets and tetany.

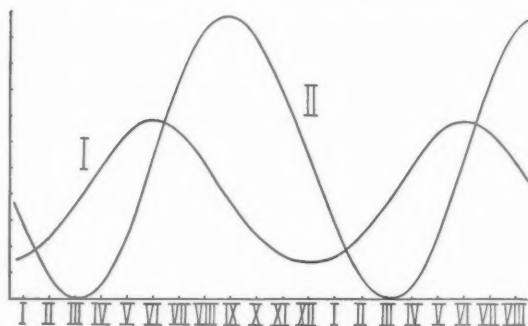


Chart 1. Abscissa: Months.

While the intensity of direct sunlight has its minimum three months before the culmination of these diseases, the accumulated effect of sunlight and the frequency curves of the cases show a complete inverse interdependence, the accumulated effect having its minimum when the case frequency reaches maximum and vice versa.

It may be objected, that the date of admission to hospital not always coincides with the beginning of the disease and that curves based upon these dates do not reflect the real conditions. To this must be remarked, that children with tetany presumably nearly always are hospitalized shortly after the disease has manifested itself. As to rickets, it is not easy to get a better criterion than that the symptoms have been so pronounced, that they demand hospitalization. Even if this takes place due to bronchopneumonia or dyspepsia, the underlying weakening of the constitution in most cases certainly has been caused by the existing rickets, and these hospitalizations therefore principally will take place, when the resistance of the organism against rickets is lowest. After all our present clinical knowledge we are bound to suppose, that the resistance against rickets is lowest, when the amount of vitamin D in the body is lowest and vice versa. Applied to the results here given, this means that manifested and presumably also relative lack of vitamin D is most frequent in March and rarest in September.

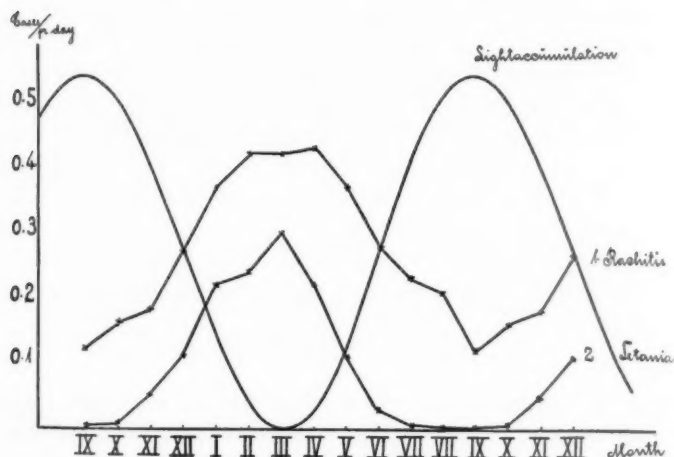


Chart 2.

Vitamin D satisfies the criteria adopted in the computation of curve II, viz. 1) formation through irradiation by sunlight. 2) capability of accumulation. 3) steady use by the organism. It is not known, whether the requirement of vitamin D is the same the year round, but we have no knowledge as to the contrary. Considering this reservation, it is suggested, that curve II approximately reflects the seasonal fluctuations of the contents of vitamin D in the infantile organism. Of course supply of vitamin D otherwise than by irradiation of sunlight might change this. As to normal food it is probable that the vitamin D contents follow the same annual variation, as in this case it presumably also originates from the effect of light.

The results arrived at show that the characteristic postponement of the maximum incidence of rickets and tetany to the spring exactly must be expected, when the diseases are caused by lack of a substance which accumulates in the body by the effect of sunlight.

Should the onset of a disease be favoured by the presence of such accumulated substance, the greatest number of cases

might be expected around the equinox of the autumn. Certain diseases, like intestinal infections and poliomyelitis, are most frequent during that period of the year. It ought to be examined, whether their occurrence has anything to do with the variation of sunlight. As to poliomyelitis, such connexion has previously been pointed out. (HELGE PETERSEN) (5).

Summary.

While the direct effect of sunlight has its maximum in June and its minimum in December, a possible accumulated effect of sunlight will reach maximum in September and minimum in March (on the northern hemisphere), provided the disintegration of the accumulated substance proceeds with the same intensity throughout the whole year.

A survey of the date of hospitalization of 1259 patients with rickets and 478 with tetany showed that these vitamin-D-deficiency-diseases had their maximum incidence around March and minimum around September. A complete reciprocal interdependence is shown by the case incidence curves and the curve showing the accumulated effect of sunlight. It is considered probable, that the seasonal variations of the vitamin D contents in the infantile organism approximately follow the latter curve.

Finally it should be underlined, that a seasonal disease may well be dependent on sunlight, even when its maximum is found around one of the equinoxes.

Table.

Monthly distribution of cases of rickets and tetany, admitted to The Childrens Hospital, Fuglebakken, during the years 1924—1935 incl.

	Rickets	Tetany
January.....	137	83
February.....	142	80
March.....	155	111

	Rickets	Tetany
April.....	155	78
May.....	139	41
June.....	102	11
July.....	85	3
August.....	79	2
September.....	44	2
October.....	58	3
November.....	62	20
December.....	101	44

Bibliography.

1. COBLENTZ, W. W.: The physical aspects of ultraviolet therapy. J. A. M. A. vol. 111: p. 419—423, 1938. — 2. GUILD, H.: Infantile tetany in Brennemann: Practice of pediatrics, vol. 1, chapt. 37, p. 3, 1939. — 3. MADSEN, TH.: The influence of seasons on infection. The Abraham Flexner lectures. Series number five, p. 123—171, 1937. — 4. OSLER, W.: Principles and practices of medicine. 12. edition (Mc. Grae edit.), p. 399. — 5. PETERSEN, HELGE: The relation between light and the epidemic curve of poliomyelitis. Acta med. scand. vol. 107: p. 282—358, 1941. — 6. SHOHL, A.: Physiology and pathology of vitamin D. J. A. M. A. vol. 111: p. 614—619, 1938.
-



ACTA PÆDIATRICA

EDITORES:

A. LICHTENSTEIN, STOCKHOLM, A. WALLGREN, STOCKHOLM

REDACTORES:

IN DANIA: BENT ANDERSEN, AARHUS, OLUF ANDERSEN, KØBENHAVN, C. E. BLOCH, KØBENHAVN, P. PLUM, KØBENHAVN. *IN FENNIA:* P. HEINIÖ, HELSINGFORS, V. RANTASALO, HELSINGFORS, C.-E. RÄIHÄ, HELSINGFORS, T. SALMI, ÅBO, ARVO YLPPÖ, HELSINGFORS. *IN HOLLANDIA:* E. GORTER, LEIDEN, CORNELIA DE LANGE, AMSTERDAM, J. VAN LOOKEREN CAMPAGNE, GRONINGEN. *IN NORVEGIA:* TH. FRÖLICH, OSLO, LEIF SALOMONSEN, OSLO, L. STOLTENBERG, OSLO, A. SUNDAL, OSLO, KIRSTEN UTHEIMTOVERUD, OSLO. *IN SUECIA:* C. GYLLENSWÄRD, UPPSALA, N. MALMBERG, STOCKHOLM, STURE SIWE, LUND, WILHELM WERNSTEDT, STOCKHOLM, Y. ÅKERRÉN, GÖTEBORG.

REDIGENDA CURAVIT

A. LICHTENSTEIN

KRONPRINCESSAN LOVISAS BARNSJUKHUS,
STOCKHOLM

Vol. XXXIII. Fasc. 3—4

30: XII. 1946

Almqvist & Wiksells Boktryckeri Aktiebolag
UPPSALA 1946

ACTA PÆDIATRICA

PROFESSOR A. LICHTENSTEIN
KRONPRINSESSAN LOVISAS BARNSJUKHUS,
30 POLHEMSGATAN, STOCKHOLM

The 'ACTA PÆDIATRICA' contain articles relating to pediatrics. These articles are published in English, French or German, according to the wishes of the author. Each number consists of about 6 printed sheets, 4 numbers forming a volume. The numbers will be issued as soon as the articles sent in can be printed. The 'Acta' is open to articles from foreign authors in all countries, if sufficient space can be found for them. Manuscripts are to be sent direct to the Editor, to whom also enquiries about the exchanging of papers are to be directed. The subscription should be forwarded to the Editor. Each volume costs 25 Swedish crowns or 25 shillings or 5 dollars.

ACTA PÆDIATRICA enthalten Arbeiten aus dem Gebiete der Kinderheilkunde. Die Arbeiten werden, je nach eigener Wahl des Verfassers, in deutscher, französischer oder englischer Sprache veröffentlicht. Jedes Heft enthält circa 6 Druckbogen; 4 Hefte bilden einen Band. Die Hefte erscheinen, je nachdem die in dieselben aufzunehmenden Aufsätze druckfertig vorliegen. Die Acta nehmen nach Möglichkeit auch Arbeiten ausländischer Verfasser aller Nationen auf. Manuskripte nimmt der Herausgeber entgegen, desgleichen Wünsche betreffs Austausch von Zeitschriften. Abonnementanmeldung bei dem Herausgeber. Preis pro Band 25 schwedische Kronen.

Les ACTA PÆDIATRICA contiennent des ouvrages du domaine de la pédiatrie. Les études sont publiées en français, anglais ou allemand au choix de l'auteur. Chaque fascicule contient env. 6 feuilles in-8°; 4 fascicules forment un volume. Les fascicules paraissent au fur et à mesure que les articles y destinés sont imprimés. Les Acta reproduisent, dans la mesure du possible, les articles d'auteurs étrangers de tous les pays. Les manuscrits doivent être expédiés à l'éditeur, à qui les demandes relativement à l'échange de journaux devront également être adressées. Abonnement chez l'éditeur. Prix par volume Cr. Suéd. 25.

ACTA PÆDIATRICA



FROM THE MEDICAL CLINIC OF SERAFIMERLASARETTET (CHIEF: PROFESSOR ANDERS KRISTENSON), THE WOMENS' CLINIC OF KAROLINSKA SJUKHuset (CHIEF: PROFESSOR AXEL WESTMAN), AND THE SURGICAL DEPARTMENT OF KRONPRINSESSAN LOVISAS VÅRDANSTALT (CHIEF: DOCENT PHILIP SANDBLOM).

Chorionic Gonadotrophin in the Treatment of Disturbances of Development in Childhood and Adolescence.

Preliminary Report.¹

By

ROLF LUFT.

Chorionic gonadotrophin is produced primarily by some part of the fertilized ovum, after it becomes embedded in the uterine wall, subsequently from the corresponding part of the placenta. The hormone production continues until detachment of the placenta. The hormone is excreted in the urine. In animal experiments it has the same effect as the pituitary gonadotrophin ICSH (interstitial cell stimulating hormone): in the ovary maturation of follicles and luteinization, in the testis stimulation of the interstitial cells but also — probably indirectly through stimulation of the hormone secretion of the interstitial cells — of the tubuli seminiferae (literature: see FEVOLD 1939, ENGLE and LEVIN 1941). Chorionic gonadotrophin has got some use in the therapy of metrorrhagia (Reiprich 1934, Novak 1938, Jacoby and Der Brücke 1940). It is, however, emphasized in «The Report of the Council on Pharmacy and Chemistry» 1940, that the hormone itself is of little therapeutical value in gynecology (see also Davis and Hellbaum 1943).

The hormone has been used in the treatment of cryptorchidism during several years. In the present paper I will also give a statement of the use of chorionic gonadotrophin in the treatment of hypogenitalism in boys and in growth disturbances.

¹ Read at the meeting of Svenska Endokrinologföreningen at Stockholm, November 23, 1945.

The Pregnyl was supplied through the courtesy of A. B. Pharmacia, Stockholm.

Cryptorchidism.

The ways of treatment in cases of undescended testicles have been and are still orchidopexy and endocrine therapy. Chorionic gonadotrophin has proved to be the most advantageous of the hormones tested. When criticizing the results of treatment one has mainly concentrated on the anatomical situation, i.e. if the testicle was found in the scrotum or not. In literature a successful result after orchidopexy is found in 50—70 % of the cases treated (see BJERRE 1935 and HANSEN 1945). The results of hormonal treatment show even greater variations (see PULLEN et al. 1942, WELLS 1943). A score of authors brought about descent in about 70 % of their cases (see NIXON 1938, BIGLER et al. 1938, HARDING 1943). On the other hand a number of authors have only received results in about 20 % of the cases (MIMPRISS 1938, THOMPSON and HECKEL 1939, ZELSON 1939, REA 1941, LAÛIN 1943). One of the reasons that cause the large variations is probably that certain series of treatment also included cases of pseudo-chryptorchidism, in which the tendency to spontaneous descent is very large.

As a comparison I can mention something about the cases of cryptorchidism, now being collected by LUFT and QVIST¹. On examining 30 cases of cryptorchidism, operated on with orchidopexy during 1925—1940, we found a complete descent in 5 cases. In further 7 cases the testicle was located higher up in the scrotum. In the remaining 18 cases the anatomical result was quite unsatisfactory. We have hitherto treated 50 cases with chorionic gonadotrophin. A descent of the testis could be induced in 9 (18 %) of these.

The object of treatment of cryptorchidism is, however, not only to induce a descent but mainly to produce a complete function of the testis. This possibility has been considered greater, if the testicles could be fixed in the scrotum. Is really

¹ The investigations were begun by the late Dr. James Hindmarsh and Rolf Luft, and are now continued by Luft and Qvist.

a disturbed testicular function found in cryptorchidism? The disturbances here referred to, concern:

1. *Spermatogenesis*. It may be considered proved, that sterility occurs in about 100 % in bilateral cryptorchidism, and that sterility is comparatively common also in unilateral cases (literature, see HANSEN 1945).

My results in this respect are in accordance with those of earlier investigators (table 1). The material is still limited. The semen analyses have been performed by Dr. ERIC NORLANDER. Analyses were made in eight cases of bilateral cryptorchidism, which had been operated on earlier. In two of these the testes were still located outside of the scrotum. No normal sperms were found in these cases. In the other six the testes were located in the scrotum, most of them, however, in the superior scrotal position. In five out of these six cases there was a decreased spermatogenesis (oligospermia, increased amount abnormal heads, decreased motility), but morphologically normal sperms were, however, found. The fifth case showed a total aspermia. *It is as yet too early to draw any conclusions from these results, i.e. if a better anatomical position of the testicles after operation is combined with a better fertility, and if this could be of guidance for therapy. This fact is being investigated.*

Nine cases of operated unilateral cryptorchidism were examined. Three of these patients had children, so semen analyses were considered unnecessary. Four of the remaining six cases showed ordinary sperm counts, while two showed signs of sperm deficiency.

2. *The Hormone Secretion*. DRIPS and OSTERBERG (1940) found an ordinary excretion of 17-ketosteroids in one case of cryptorchidism. *The author in his cases (table 2) found a normal excretion of 17-ketosteroids in 19 out of 21 cases.* It is remarkable, that the excretion of 17-ketosteroids was normal even in cases with defective spermatogenesis. In two cases both the hormone excretion and the spermatogenesis were deficient. *Thus a deficient spermatogenesis does not exclude a normal hormone excretion.* A dissociation of the two testicular functions is also known since long (see DESCLIN, MARTINS and DE MELLO 1935).

Table 2.
Excretion of 17-Ketosteroids in

Case	Born	Retentio- testis	Opera- tion	Investigation 1945		17-Ketoste- roids mg/day
				Testis dx	Testis sin	
1. LBH.	1907	Right	1940	Not palp.	Norm. Ser.	28,3
2. SBA.	1923	»	1926	Extirp.	Enlarged. Ser.	24,0
3. LEH.	1917	»	1939	Intraabd.	Norm. Ser.	26,3
4. LAB.	1926	»	1937	Atrophy. not palp.	Enlarged. Ser.	25,1
5. KLF.	1924	»	1938	» Reg. ing.	Norm. Ser.	24,0
6. GGF.	1925	»	1935	Small. (Ser.)	» »	31,0
7. IEL.	1928	»	1937	Atrophy. (Ser.)	Enlarged. Ser.	24,0
8. UJL.	1926	Left	1937	Norm. Ser.	Atrophy. (Ser.)	8,2
9. HGJ.	1929	»	1938	Enlarged. Ser.	Small. Reg. ing.	18,2
10. BGJ.	1922	Right	1935	Not palp.	Norm. Ser.	30,0
11. NAL.	1925	»	1937	Atrophy. (Ser.)	» »	35,0

Daily excretion of 17-Ketosteroids in healthy men: $24.8 \text{ mg} \pm 1.43$ (LUFT 1944).

The skeletal development was examined by X-rays in 40 cases. The investigations in all cases included the shoulder-, elbow-, hip-, knee-, wrist- and ankle joints. The estimation of skeletal age was conducted according to RUCKENSTEINER (Die normale Entwicklung des Knochensystems im Röntgenbild, 1931). In all cases the skeletal age was in accordance with the chronological age, i.e. skeletal development lay within the limits, considered normal for the age group in question. Nor was there in these cases any disturbed proportionality in growth between the parts of the skeleton of the body and the extremities (eunuchoid habitus), that is supposed to occur after long-standing depression of androgen production during adolescence.

As malignity of the undescended testis only occurs in 2—4 % of the cases (REA 1941, CAMPBELL 1942), the prevention of sterility becomes the main object of our efforts to bring about descent. It is emphasized in literature, that degenerative changes

2.
21 Cases of Cryptorchidism.

Case	Born	Retentio testis	Operation	Investigation 1945		17 Ketoste- roids mg/day
				Testis dx	Testis sin	
12. KGL.	1926	Left	1934	Norm. (Scr.)	Not palp.	30,6
13. SHN.	1922	Bilat	1935	» »	Small. (Scr.)	30,0
14. SJJ.	1927	»	1934	Small. (Scr.)	» »	26,1
15. GEE.	1928	»	1940	» »	» »	22,5
16. CAA.	1898	»	1943	Intraabd.	Not palp.	32,5
17. KSL.	1909	»	1944	Atrophy. Reg. ing.	» »	31,0
18. GHG.	1922	»	1935	Small. (Scr.)	Small. Scr.	26,7
19. RHD.	1928	»	1934	Norm. Scr.	Norm. Scr.	11,3
20. JÄB.	1933	»	1938	Small. Reg. ing	» (Scr.)	13,5
21. SAA.	1919	»	1923/1937	Not palp.	Small. Scr.	20,4

Daily excretion of 17-Ketosteroids in boys, see LUFT 1945.

in ectopic testicles only occur during puberty and after (REA 1941, JASON 1944). Sterility could thus in certain cases be prevented, if a fixation of the testicles in the scrotum were possible before puberty. Only orchidopexy is insufficient in many cases to prevent sterility (HANSEN 1945). Thus treatment with chorionic gonadotrophin remains, but this hormone brings about a descent only in a limited number of cases.

When we in spite of this still suggest treatment with chorionic gonadotrophin, it is for the following reasons (the authors mentioned below are of the same opinion as myself):

1. Hormone treatment shows if the case is suitable for this form of therapy or if there are anatomical obstacles to the descent (THOMPSON et al. 1937, REA 1941, FREED 1942, LAPIN et al. 1943, HARGING 1943). In the cases where we were successful, the descent occurred already after seven injections of Pregnyl,

each containing 600 I.E. In such cases where seven injections were insufficient, a descent could not be induced even if the injections were continued for a long time.

2. In spite of the fact that in most cases a full descent was not obtained, a partial descent was obtained (in 35 cases out of 40), i.e. a movement of the testis towards the scrotum.

3. In a number of cases (7 out of 10) an unpalpable testicle was made palpable by pre-operative treatment with chorionic gonadotrophin.

4. The subsequent operation is considerably facilitated by the pre-operative treatment with chorionic gonadotrophin. This treatment seems to bring about an elongation of the funicle and an improved development of the scrotum (THOMPSON *et al.* 1937, REA 1941, HARDING 1943, LAPIN *et al.* 1943). The reason may be that the hormone stimulates the production of male hormone in the testicles.

5. Orchidopexy should be followed by a post-operative treatment with chorionic gonadotrophin in order to stimulate testicular function and to induce a firmer fixation of the testicles in the scrotum (LAPIN *et al.* 1943).

In the following I will give an account of the treatment of hypogenitalism and growth disturbances with chorionic gonadotrophin.

Hypogenitalism in Boys.

The effect of testosterone propionate and methyl testosterone on genital growth and development of secondary sex characteristics is well known (complete literature: see HAMILTON 1937, MC CULLAGH and ROSMILLER 1941, FAGER 1942, GORDON and FIELDS 1943, LISSER 1943, VEST and BARELARE 1943, KENYON *et al.* 1944, BAYER 1944). With these hormones satisfactory results have been obtained in the treatment of hypogenitalism due to primary testicular insufficiency as well as to hypogenitalism

due to inadequate stimulation of the testes from the pituitary. But these hormones should be used with caution in the treatment of similar disturbances during puberty and adolescence. Some investigations indicate that large doses of testosterone preparations may induce a precocious closure of the epiphyses (FANCHER 1932, McCULLAGH and MACGURL 1940, GOLDZIEHER 1941, HURXTHAL 1943) and sometimes even atrophy of the testes (MOORE and PRICE 1938, SHAY et al. 1941, RUBINSTEIN and KURLAND 1941, SELYE 1943, McCULLAGH 1943). Chorionic gonadotrophin seems to be the adequate hormone in the treatment of male hypogenitalism during childhood and adolescence. Though some successful therapeutic attempts have been reported (GORDON and FIELD 1942, PULLEN et al. 1942, FINKLER and COHN 1943), the experience of this method of treatment seems to be rather poor.

Rather early there occurred growth of the penis and obvious growth of pubic hair in most cases of cryptorchidism during treatment with chorionic gonadotrophin. The stimulation was so strong in some cases that the treatment had to be discontinued for the time being. The changes then disappeared, however.

The author has used chorionic gonadotrophin on five boys with hypogenitalism. The patients were 10—17 years old. The results were satisfactory in four out of these five cases. The fifth one was a boy of 16, that since three years had a complete testicular atrophy of traumatic origin. Chorionic gonadotrophin was of no use in this case, but with large doses of testosterone propionate a beginning eunuchoidism could be checked.

The following case may be representative for the cases of hypogonadism that were successfully treated with chorionic gonadotrophin.

Case 1. (P. E. D., born 1930, figs. 1—2.) Boy of 15. Already as a child he was very fat and dysplastic. Gymnastics were too much for his strength, but otherwise he followed his schoolwork sufficiently well. In 1942 bilateral cryptorchidism and marked genital hypoplasia were diagnosed. Large doses of serum gonadotrophin (a total of 24 000 I.E.) were injected during June 1942—December 1943 without any remarkable effects. Spontaneous descent of testes occurred in 1944. During the last year more rapid height increase. On examination in August

1945 (fig. 1): A rather tall, pale boy of the Fröhlich type with very small penis (4 cm.), full breasts, girdle type obesity, broad hips and large thighs. Testes as hazel-nuts in size, scrotum badly developed. Voice feminine. Prostate very small. No hair growth on extremities, in the face or on



Fig. 1. Boy. 15 years old, with hypogonadism.



Fig. 2. Same boy as in fig. 1 after 3 months treatment with Pregnyl.

the trunk, but a slight hair growth on the large mons veneris. Body length 173 cm, weight 91,5 kg, span 180 cm. lower measurement 90 cm, chest 99 cm, abdomen 89 cm, hip measure 118 cm. B. M. B. — 10 %. Skeletal development on X-rays corresponded to an age of 15 years. *Therapy:* Pregnyl 600 I.E. twice a week during two months.

On examination in October 1945 a marked improvement was noticed. The boy felt stronger, was more active, which has been noticed by parents and teachers. Body shape had changed, adiposity had de-

creased, which may be seen by the following measurements: height 174 cm, weight 86 kg, span 180 cm, lower measurement 90 cm, chest 96 cm, abdomen 80 cm, hip measure 112 cm. The penis had nearly reached normal size (7.5 cm), the testes were twice as large as before treatment, the scrotum too had noticeably increased in size. There was now a slight hair growth on body, extremities, cheeks and upper lip, as well as a marked development of pubic hair. On examination in November (fig. 2) the improvement was found to have proceeded. The patient's voice was now breaking.

Excretion of 17-ketosteroids: before treatment in August 1945 9 mg/day, in October 23 mg (normal value) and in November 28 mg a day.

Growth Disturbances.

During the last years great attention has been paid to the connection between gonadotrophic hormones and somatic growth. Several authors have found a growth-promoting effect in small doses of testosterone and testosterone propionate (GOLDZIEHER 1939 and 1941, RUBINSTEIN and SOLOMON 1940, RAPFOGEL 1940, WEBSTER and HOSKINS 1940; McCULLAGH and ROSMILLER 1940 as regards methyl testosterone). The growth-promoting effect of chorionic gonadotrophin was first noticed during the treatment of cryptorchidism and hypogonadism. During the war years it has been used in America with success in cases of growth disturbance. (DORF 1940—41, LURIE and HERTZMAN 1941, GORDON and FIELDS 1942—43).

My material consists of three boys aged 15—17 years, suffering from retarded growth. Two of these also showed hypogonitalism. I also treated two girls with pituitary dwarfism. None of these five cases had any clinical signs of hypothyroidism. In all these cases the treatment was initiated with thyroid hormone during 1—2 months, with no effect, however. Three of these cases will be reported here.

Case 2. (A. H., born 1928.) Boy of 16. According to statements from the parents ordinary bodily development until 12—13 years of age (1940—41). At this very time growth as well as bodily and genital development seem to have come to a standstill. Height 151 cm in 1942, 152 cm in 1943 and September 1944. On examination in September

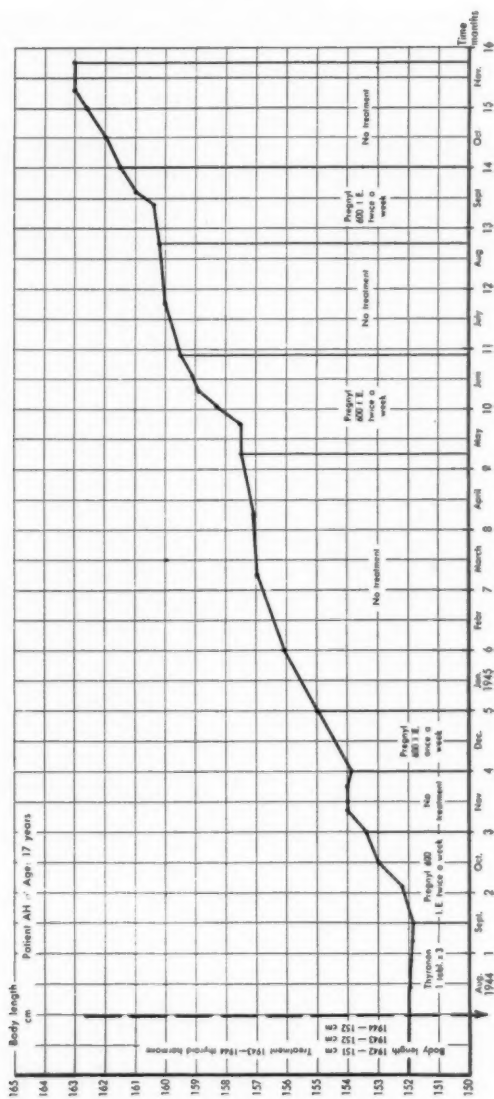


Fig. 3.

1944: Small boy with infantile appearance. Bodily as well as genital development corresponded to an age of 13. Penis very small, testes the size of hazel-nuts, no signs of hair growth on body, extremities, in the face or on the pubic region. His voice had not yet broken. Physically he was childish. Could not manage his school-work during last three years and failed to get his removal to the next class.

Therapy (see fig. 3): Had received thyroid preparations during the last year with no effect. Pregnyl treatment was now begun according to the graph fig. 3. There was a prompt reaction to the treatment. Height increased 11 cm during one year; weight increased from 43 to 50 kg; the voice became masculine; bodily development perceptibly increased. The penis and testes became almost normal in size. A marked pubic and axillary hair growth appeared. There was a psychical maturity and he could follow his schoolwork much easier. The favourable therapeutic effect seems to continue.

Excretion of 17-ketosteroids: in September 1944 9 mg, in May 1945 21 mg a day.

Case 3. (H. F. B., born 1930.) Boy of 15. Had always been shorter in stature and of weaker constitution than his comrades. Height increase was continuing all the time but rather slowly. Now the patient was supposed to go into business but it was difficult for him to get a job because of his small size. Height was 148 cm, weight 41,6 kg, span 152 cm, lower measurement 77 cm. He showed a rather infantile appearance. As a contrast to this was an ordinary development of penis, scrotum and testes. Pubic and axillary hair growth were, however, missing. Intelligence age 15-16 years.

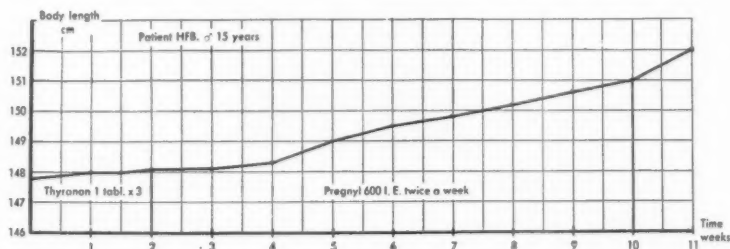


Fig. 4.

Treatment (fig. 4): Thyroid therapy during three weeks was unsuccessful; there was only a slight height increase but the duration of treatment with thyroid preparations was too short to allow of any definite conclusions. Chorionic gonadotrophin was then substituted and Pregnyl

600 I. E. was given twice a week. The treatment has now been given during 11 weeks, and the patient has grown 4 cm, while weight has increased 2 kg. Pubic hair growth has begun to appear.

Case 4. (A. S. V. N., born 1929, fig. 5.) Girl of 16 with the typical picture of pituitary dwarfism.



Fig. 5. Girl of 16 with pituitary dwarfism.

This girl seems to have developed normally until about 7 years of age. When sent to school she was smaller than her schoolfellows. Bodily development was then retarded and growth ceased. She went through the school, managing fairly well. Then she went in for household work, and is now working as housemaid. On the first examination in *February 1945*, when 16 years old, height was 132 cm, weight 29 kg. The span and height were equal and so were the upper measurement and the lower.

There was very little subcutaneous fat and no pads of fat. She was well-proportioned, but bodily development corresponded to 8 years of age. Genitals infantil on gynecological examination, no development of breasts. She seemed to be rather clever, but had a very limited sphere of interest. The development of the epiphyses corresponded to a child of 12 years of age.

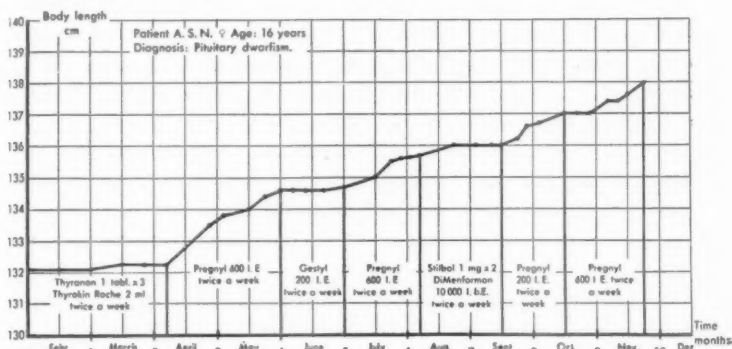


Fig. 6.

Treatment (fig. 6): Treatment with thyroid preparations (Thyranon 1 tabl. \times 3 and Thyroxin Roche 2 ml twice a week) did not give any remarkable stimulation of growth. The stimulation was, however, obtained with Pregnyl (600 I. E. twice a week), while there was no remarkable height increase during periods, when serum gonadotrophin (Gestyl), estradiol benzoate (DiMenformon) and Stilbol were substituted. The total height increase was 6 cm during April—November 1945, but during this time the chorionic gonadotrophin was omitted for three months and replaced by less active substances. The effective time of treatment was 5 months.

Excretion of 17-ketosteroids: before treatment 10—11 mg a day. After one, two and three weeks of treatment with 600 I. E. Pregnyl twice a week still 10—11 mg a day.

These three cases may illustrate the growth stimulating effect of chorionic gonadotrophin. This is most evident in the girl with pituitary dwarfism, since this disease otherwise is very resistant to therapy (methyl testosterone, however, used with success by Wagner 1943, chorionic gonadotrophin in connection with male hormone by THOMPSON et al. 1944). The interpreta-

tion of the stimulative effect is rather uncertain. It can as yet not be decided, if the chorionic gonadotrophin has a primary growth stimulating effect or if this is secondary to a stimulation of the gonads.

In the boys with growth disturbances there was an enlargement of the testes during the treatment. In cases 1 and 2, where determinations of the urinary 17-ketosteroids were performed, these substances were increased in connection with the gonadal stimulation. In case 6, the dwarfed girl, the urinary 17-ketosteroids were unchanged after treatment.

This stimulative effect of chorionic gonadotrophin is of special importance now, since the growth hormone of the anterior pituitary has not proved to be so favourable in growth disturbances, as it was at first supposed to be (SHELTON 1942, RYNEARSON 1944).

At which age should the treatment of disturbances of development start? On one hand there is often a spontaneous improvement of cryptorchidism, hypogonadism or growth disturbances, particularly at puberty. On the other hand our chances to remove a disturbance of development are much greater, when the child is younger and the skeleton less differentiated. It is therefore at the same time a difficult and an important task for the physician to decide on the right moment for treatment.

It is an old moot question when to start treatment in cryptorchidism. This question shall be the object of discussion in a later article. When treating cases with moderate disturbances of genital and bodily development, I always try to wait for the arrival of puberty. Treatment was therefore mostly begun at the age of 15—16. In severe cases, however, the treatment was started immediately, irrespective of age.

Conclusion. Chorionic gonadotrophin seems to be a hormone with considerable power to restore the normal bodily development in cryptorchidism, hypogonadism and growth disturbances. It ought to become of great use in the treatment of these disturbances in childhood and adolescence.

The author gives preliminary reports on some investigations

of the use of chorionic gonadotrophin in the treatment of cryptorchidism, hypogenitalism and growth disturbances. The main features of these investigations are:

The spermatogenesis was examined by means of semen analyses in 17 cases of cryptorchidism, nine unilateral and eight bilateral ones, that had been operated on earlier. There was a sperm deficiency in two cases of unilateral and in all cases of bilateral cryptorchidism. The deficiency was less pronounced in those cases of operated bilateral cryptorchidism, in which the testes at re-examination were found in the scrotum, than in those where the testes were unpalpable or palpable in regio inguinalis.

The excretion of urinary 17-ketosteroids was within normal limits in 19 of 21 cases of cryptorchidism.

In all cases skeletal age on X-rays corresponded to chronological age.

Other forms of disturbances of development did not appear more often in cryptorchidism than in the ordinary patients visiting the outpatient department.

Thirty operated cases of cryptorchidism were re-examined (by LUFT and QVIST). The testes were found in the ordinary scrotal position in five and in the superior scrotal position in another seven of these cases.

Fifty cases of cryptorchidism were treated (by LUFT and QVIST) with chorionic gonadotrophin. A complete descent was induced in nine cases (18 %), while a partial descent was evoked in most cases.

The author suggests that treatment in cryptorchidism should always start with chorionic gonadotrophin; operation should be resorted to in those cases where a complete descent can not be induced by hormone treatment. The operation is followed by post-operative treatment with chorionic gonadotrophin.

Five cases of hypogenitalism in boys have been successfully treated with chorionic gonadotrophin. The author gives a report on one of these cases.

Chorionic gonadotrophin remarkably stimulated bodily development and growth in two boys, 15 years of age, with growth disturbances, and in a girl of 16 with pituitary dwarfism.

Treatment with chorionic gonadotrophin in one boy with hypogonitalism and another with growth disturbance was connected with an increased excretion of urinary 17-ketosteroids at the same time as an enlargement of the testes. No such increase was concomitant to the same treatment in the dwarfed girl.

References.

- BAYER, L. M., *J. Clin. Endocrinology* 1944, 4: 297. — BIGLER, J. A., L. M. HARDY, and H. V. SCOTT, *Am. J. Dis. Child.* 1938, 55: 100, 273. — BJERRE, H., *Kliniske Undersøgelser over Ingvinkryptorchismen hos Mennesket*, Disp. København 1935. — CAMPBELL, H. E., *Arch. Surg.* 1942, 44: 353. — DAVIS, M. E., and A. A. HELLBAUM, *J. Clin. Endocrinology* 1943, 3: 517. — DESCLIN, L., *Archives de Biol.* 1934, 45: 503. — DORFF, G. B., *Endocrinology* 1940, 27: 403. — DORFF, G. B., *J. Clin. Endocrinology* 1941, 1: 940. — DRIPS, D. G., and A. E. OSTERBERG, *Endocrinology* 1940, 27: 345. — ENGLE, E. T., and L. LEVIN, *J. A. M. A.* 1941, 116: 47. — FANCHER, T. K., *Endocrinology* 1932, 16: 611. — FEVOLD, H. L., *Endocrinology* 1939, 24: 435. — FINKLER, R. S., and G. M. COHN, *Arch. Pediatr.* 1943, 60: 362 (ref.). — FREED, S. C., *Illinois M. J.* 1942, 82: 165 (ref. *J. Clin. Endocrinology* 1943, 3: 187). — GOLDZIEHER, M. A., *The Endocrine Glands*, New York 1939 (ref.). — GOLDZIEHER, M. A., *J. Clin. Endocrinology* 1941, 1: 924. — GORDON, M. B., and E. M. FIELDS *J. Clin. Endocrinology* 1942, 2: 531. — GORDON, M. B., and E. M. FIELDS, *Ibid.* 1942, 2: 715. — GORDON, M. B., and E. M. FIELDS, *Ibid.* 1943, 3: 589. — HAMILTON, J. B., *Endocrinology* 1937, 21: 461. — HANSEN, T. S., *Fertiliteten ved operativt behandlet og ubehandlet Kryptorchism*, Disp., København 1945. — HARDING, F. E., *J. Pediatr.* 1943, 23: 45 (ref. *J. Clin. Endocrinology* 1944, 4: 92). — HURXTHAL, L. M., *J. Clin. Endocrinology* 1943, 3: 12. — IASON, A. H., *Am. J. Surg.* 1944, 105: 353. — JACOBY, A., and M. G. DER BRÜCKE, *Am. J. Obst. & Gynec.* 1940, 39: 509. — KENYON, A. T., K. KNOWLTON, and I. SANDIFORD, *Ann. Int. Med.* 1944, 20: 632. — LAPIN, I. H., W. KLEIN, and A. GOLDMAN, *J. Pediatr.* 1943, 22: 175. — LISSER, H., *J. Clin. Endocrinology* 1943, 3: 613. — LUFT, R., *Hirsutism, Cushings Syndrome . . .*, Acta med. scand., Suppl., 1944. — LUFT, R., *Nord. Medicin* 1945 (in press). — LURIE, L. A., and J. HERTZMAN, *J. Clin. Endocrinology* 1941, 1: 717. — MARTINS, T., and R. F. DE MELLO, *Compt. rend. Soc. Biol. Paris* 1935, 118: 916. — McCULLAGH, E. P., *J. Clin. Endocrinology* 1943, 3: 375. — McCULLAGH, E. P., and F. I. GURL, *Endocrinology* 1940, 26: 377. — McCULLAGH, E. P., and H. R. ROSMILLER, *J. Clin. Endocrinology* 1941, 1: 50, 496, 507. — MIMPRISS, T. W., *Lancet* 1938, 1: 533. — MOORE, C. R., and D. PRICE, *Anat. Rec.* 1938, 71: 59. — NIXON, N., *Am. J. Dis. Child.* 1938, 55: 1037. — NOVAK, E., *Texas State J. Med.* 1938, 34: 263. — PULLEN, R. L., J. A. WILSON, E. C. HAMBLIN

and W. K. CUYLER, *J. Clin. Endocrinology* 1942, 2: 577, 655, 730. — RAFFOGEL, I., *Endocrinology* 1940, 27: 179. — REA, C. E., *Internat. Clin.* 1941, 4: 262. — REIPRICH, W., *Zschr. f. Geburtsh. u. Gynäk.* 1934, 109: 285. — Report of the Council on Pharmacy and Chemistry, *J. A. M. A.* 1940, 39: 509. — ROSINSKY, O. E., *Med. Klin.* 1942, 38: 843. — RUBINSTEIN, H. S., and A. A. KURLAND, *Endocrinology* 1941, 28: 495. — RUBINSTEIN, H. S., and M. L. SOLOMON, *Proc. Soc. Exp. Biol. & Med.* 1940, 44: 442. — RUCKENSTEINER, E., *Die normale Entwicklung des Knochensystems im Röntgenbild*, G. Thieme, Leipzig 1931. — RYNEARSON, E. H., *J. A. M. A.* 1944, 125: 5. — SELYE, H., *Endocrinology* 1943, 32: 116. — SHAY, H. I. GERSHON-COHEN, K. E. PASCHKIS, and S. S. FELS, *Endocrinology* 1941, 28: 485. — SHELTON, E. K., *Endocrinology* 1942, 30: 1000. — TAGER, B. N., *J. Clin. Endocrinology* 1942, 2: 107. — THOMPSON, W. O., *Nebraska M. J.* 1943, 28: 9 (ref. *J. Clin. Endocrinology* 1943, 3: 385). — THOMPSON, W. O., and N. T. HECKEL, *J. A. M. A.* 1939, 112: 397. — THOMPSON, W. O., N. T. HECKEL, A. D. BEVAN, and P. K. THOMPSON, *Tr. A. Am. Phys.* 1937, 52: 137. — THOMPSON, W. O., N. T. HECKEL and P. K. THOMPSON, *Endocrinology* 1944, 35: 222. — UFFREDUZZI, O., *Arch. Klin. Chir.* 1913, 101: 150. — WAGNER, R., *New England J. Med.* 1943, 229: 737. — WEBSTER, B., and W. H. HOSKINS, *Proc. Soc. Exp. Biol. & Med.* 1940, 45: 72. — WELLS, L. T., *Surgery* 1943, 14: 437. — VEST, S. A., and B. BARELARE, *Clinics* 1943, 1: 1216. — ZELSON, C., *J. Pediatr.* 1939, 14: 452.

FROM THE UNIVERSITY PEDIATRIC CLINIC, RIKSHOSPITALET, OSLO.
CHIEF: PROFESSOR LEIF SALOMONSEN.

The acute leukemia in children.

By

JOHAN RIIS.

As our experiences widen and the diagnostic aids become increased in number and subtlety it happens that a disease changes in appearance, indeed, it may take on an entirely new face. — This is partly because we have succeeded in recognising the disease at an earlier time, before the classical symptoms have had the chance to develop, partly because we have become able to diagnose also less typical forms of the disease.

Recollecting what was meant by »tuberculous diseases» half a century ago and the meaning of it today, the development at once will be clear. The tuberculin test, culture of the tubercle bacillus, inoculation upon animals, the sedimentation reaction and particularly the roentgen examination have radically changed the picture of the tuberculous diseases.

Infarctus cordis, by the elders of clinicians called »status anginosus», no longer is diagnosed exclusively on the anamnesis and on rough clinical symptoms. Equal importance is attributed to the electro-cardiogram, the leukocyte count, the sedimentation rate, eventual residue N values and the blood sugar values. Myocardial infarction today has a varied facies morbi, in which gastrointestinal symptoms, pulmonary symptoms or symptoms of acute circulatory failure may dominate. In some cases all the classical symptoms are lacking.

A similar development has taken place for the diseases of the blood. The anemias are differentiated into a number of defined facies morbi. However, here probably only beginning of the de-

velopment has been reached. This particularly applies to anemia in children where the pathogenetic factors have been far from satisfactorily investigated.

The leukemic diseases have been taken up for renewed studies since our extended knowledge of morphology of the white blood cells and the sternal puncture as additional diagnostic aid have improved on our qualifications. The consequence is that the symptomatology of the leukemic diseases has changed. This especially holds for the acute leukemias.

The acute leukemias still in the textbooks are described as diseases following an acute course, with high fever, hemorrhagic diathesis, necroses in larynx and oral cavity and having a rapid course. A number of monographies from recent years have shown that this description of the disease is not consistent with the actual conditions, but only applies to the terminal stages of the disease. Amongst publications from the Scandinavian countries, that are of special interest, there are OLE K. EVENSEN and HALL SCHAR-TUM-HANSENS work of 1941, and OLOF BRANDBERGS thesis for the doctorate of 1943. In the following references will be made to these works. In the present publication it will be accounted for 24 cases of acute leukemia collected from the Pediatric Department of the University Hospital during the years 1937 to October 1944.

Physiologically the hematology of the child during the first days after birth is characterised by high numbers of white blood cells, 15 000 to 30 000 per mm³, with 60 %—70 % of polynuclear cells. In course of the following days the number rapidly falls to about half, as especially the polynuclear cells are reduced, and a relative lymphocytosis arises. From about the age at which the child begins at school the number of the white blood cells is the same as in the adult.

In 1922 NAEGELI wrote: »Myeloische Leukemi ist sehr selten und vor dem 4. Lebensjahre nicht beobachtet.» This conception is no longer maintained, but the acute leukemia still is a comparatively rare disease. The two first cases of acute myelogenous leukemia in children in the Scandinavian literature were published by N. MALMBERG in 1925. JEAN V. COOKE finds 50 cases

of acute leukemia in about 100 000 admissions. He finds a decided increase in late years. WALLSTEIN and BARLETT collected 14 cases from a material of 24 246 patients, BRANDBERG 34 from amongst 14 628 patients. All these statistics are dealing with children. At the Pediatric Department of the University Hospital 24 cases of acute leukemia have been diagnosed in course of the period 1/2 1937 to 1/10 1944. During this same period a total of 5 019 patients have been treated. However, these numbers give no representative picture of the frequency of the disease, as the department to no small extent is being used as diagnostic department to a selected material of patients from all over the country.

In the present material of 24 children there are 15 boys and 9 girls. This surplus in the number of boys corresponds to what usually is found in larger statistics. However, BRANDBERG finds an even distribution. JEAN V. COOKE's material consists of 32 girls and 18 boys.

Distribution as to age is seen from the following table:

Age in years	0—1	1—2	2—3	3—4	4—5	5—6	6—7	7—8	8—9
Number of pts.	2	3	5	4	4	2	2	1	1

It appears that 3/4 of the material is found in the ages 0—5 years. RAMSEY found the number of leukemias in children of the ages 0—4 to be twice the number found in the next 4 years. In WILLIS collective statistics most patients are found in the group of 3—4 years of age. BRANDBERG finds an even distribution throughout childhood. The youngest patient in the present material was 5 months old when the diagnosis was made.

The patients have been admitted to the department under various diagnoses: Leukemia 9 patients, Anemia 4 patients, Acute rheumatism 2 patients, Scorbutus with anemia 2 patients. In 2 cases there is no diagnosis, otherwise the following diagnoses have been represented, each with one case: Adenitis colli with articular pain, Mongolism, Broncho-pneumonia, Disease of the blood, Observation.

The material of Ole K. Evensen and Hall Schartum-Hansen (E. & S. H.) includes 22 patients in the ages 2.5 to 71 years. Of these patients 6 are below 10 years of age. The admission-diagnosis of leukemia has only been used for 3 of these 22 patients, whereas anemia as admissiondiagnosis occurs in more than half the number of cases. Possibly this is attributable to the more rapid development of the disease in children compared to in adults, whereby the typical symptoms appear sooner. The rapid development in childhood is emphasised by E. & S. H.

The initial symptoms in the present material are for a great part hardly marked and diagnostically valuable. The patients have consulted a physician for averagely 2 to 3 symptoms. If these are put into table form, the following will be seen:

Fatigue is initial symptom in.....	12	patients
Lack of appetite.....	9	»
Pallor.....	8	»
Fever.....	7	»
Glands on the neck.....	7	»
Articular pain.....	4	»
Bleedings in skin and in mucosa.....	4	»
Infections (orchitis, otitis).....	3	»
Enlarged inguinal glands.....	2	»
Enlarged axillary glands.....	1	»
Skin-infiltrates.....	1	»
Stomatitis.....	1	»
Swelling around the eyes.....	1	»

Fatigue, lack of appetite, pallor and fever thus are amongst the most frequent initial symptoms. Next there are found enlarged glands on the neck in 7 out of 24 patients. In E. & S. H.'s material considerable glandular enlargement is the initial symptom in one of the patients only. It seems as if this symptom is considered to be of special diagnostic significance, as all the 7 patients mentioned above have been admitted under the diagnosis of leukemia. The remaining two patients who have been admitted under this diagnosis have offered either marked pallor or en-

Pat. No.	Enlargement of	Liver	Spleen	Axil. gl.	Gl. on neck	Inguin. gl.
1				x	x	x
2		x		x		
3		x	x		x	x
4				x		x
5		x	x			
6			x			
7		x	x	x	x	x
8		x	x			
9		x		x	x	x
10				x	x	x
11		x	x		x	x
12				x	x	
13		x	x		x	x
14			x	x	x	x
15		x	x			
16		x		x	x	x
17				x	x	x
18						
19		x		x	x	x
20		x	x		x	
21			x	x	x	x
22					x	
23				x	x	x
24		x	x	x	x	x

larged liver and spleen as the most important symptoms. The relatively frequent occurrence of glandular enlargement in children compared to in adults may thus explain why already on admission the diagnosis has been made oftener in this material than in that of E. & S. H.

In the patients are found glandular tumor, spleen- or liver-tumor as very usual symptoms. That the spleen- and liver-tumors are *real* is supported partly by the description on ad-

mission, partly by the liver or spleen growing even larger during the stay, or is found enlarged on section. Only in one case it is possible that the palpable liver represents a physiologic finding. See the table p. 234:

On admission it is thus seen: Enlarged glands on the neck: 17 times, enlarged inguinal glands: 15 times, enlarged axillary glands: 14 times, enlarged liver: 13 times (12?), enlarged spleen: 12 times.

Only in 1 case have all these symptoms been lacking on admission. Liver- spleen- or glandular enlargement therefore are frequent symptoms in the acute leukemia in children. The enlargements vary from the slightest to the most severe degrees. As it is also a relatively early symptom great importance should be attached to it. In comparison to what has been told above it may be mentioned that E. & S. H. in 1 patient only found considerable swelling of the glands on the neck, in 9 cases slight enlargement, whereas the spleen was found enlarged in 9 cases and the liver in 12 cases.

The hemoglobine values when the diagnoses were made appear from the table p. 236 (for case No. 24 determination of hemoglobin is lacking).

It is seen that the hemoglobin value at the time when the diagnoses were made lies below 70 % in 18 out of 23 cases. In 14 cases there is a considerable anemia with hemoglobin values below 50 %. The lowest value observed is 18 %, the highest 95 %. Schulten claims that the index as a rule lies below 1.

In the present material index is as follows: In 9 cases it is above 1, in 3 cases it equals 1, in 11 cases it lies below 1.

Index varies between 0.7 and 1.8. In 20 of the 23 cases the values lie between 0.8 and 1.2. In 4 cases no anemia is shown at the time when the diagnosis is made. The hemoglobin values in these cases vary between 75 % and 95 %, and index lies between 1.1 and 1.2. In anemias below 30 % index varies from 0.7 to 1.8.

In the 4 patients who were not anemic to begin with the following will be found: In patient No. 13 the hemoglobin percentage has fallen from 92 % to 38 % 6 weeks after the first hemoglobin determination, and index from 1.2 to 0.7. The three others have been under observation from 1 to 6 weeks (Patients Nos 3, 4 and

Patient No.	Hgl. value	Index
1	27 %	1.1
2	29 %	1.5
3	95 %	1.1
4	75 %	1.1
5	69 %	0.9
6	24 %	1.0
7	45 %	0.8
8	25 %	0.9
9	29 %	1.15
10	43 %	1.0
11	55 %	0.8
12	69 %	1.0
13	92 %	1.2
14	24 %	0.7
15	48 %	0.8
16	62 %	0.95
17	80 %	1.1
18	16 %	0.9
19	20 %	0.8
20	35 %	0.8
21	71 %	1.2
22	38 %	0.8
23	25 %	1.8

17). No distinct fall in the hemoglobin percentage has been shown during this period. From the appearance of the first symptoms these 4 patients have been under control from 4 to 9 weeks without the hemoglobin percentage falling below 75 %. Therefore anemia should be characterised as a frequent, but not as a necessary symptom. It may be lacking for several weeks after the diagnosis has been made. Index offers no clues for the diagnosis.

The number of white blood cells at the time of the patient's admittance to the department shows highly varying values, from 1300 up to 185 000 per mm^3 of blood. Only 2 cases show extre-

mely high values of white blood cells, about 200 000 per mm³. The values appear from the table:

Number of white blood cells per mm³ of blood:

	Below 5 000	5—10 000	10—20 000	20—30 000	Above 30 000
Number of patients	12	5	4	1	2

The present material thus shows 50 % of the cases with values below 5 000. In 3 cases only — the patients' ages considered — the values are distinctly increased (above 20 000). In 4 cases the increase is doubtful and probably within limits of the physiological variations. In 17 cases there are certain normal or even reduced values in the numbers of white blood cells.

During the stay the number of white blood cells varies in the individual patient. This variation has been pointed out by several authors, e. g. by E. & S. H., KIRSCHBAUM and PREUSS et al. In one case in the present material the number of white blood cells falls from 17 000 to 5 400 and in another case it rises from 4 100 to 29 000 per mm³. These numbers represent the extreme variations.

5 patients have had painful articular tumors. Of these 2 have been admitted under the diagnosis of acute rheumatism. Skeletal symptoms never have occurred, at least not as initial symptom. In 7 patients from E. & S. H.'s material articular symptoms are found at some time or other in course of the disease, 5 times as initial symptom. 4 times the disease commenced with skeletal pain, especially in the lower extremities. It has been pointed out that these symptoms mostly are seen in young individuals. In E. & S. H.'s material articular and skeletal symptoms are thus found in half the number of cases, whereas the present material only shows 5 patients with articular symptoms.

In 17 patients roentgenograms of the osseous system have been taken, the examination is not complete however. In 11 of these cases no pathologic changes were found, in 1 case *possibly* slight changes. In 5 patients there were certain pathologic findings. These may all be fitted into a schedule put up by Olof Brandberg,

namely: 1) Periosteal depositions, 2) Disseminated destruction foci, 3) Clearings or rarefaction foci in metaphysis of the long bones, 4) Osteosclerosis. On closer roentgenologic examination it is possible that further cases of pathologic changes might be exposed.

E. & S. H. found roentgenologic skeletal changes in 4 cases. However, they believe that these findings will be more common after more systematic examinations. Put together, their material and the present one show roentgenologic changes in 9 cases out of 46. As this represents a minimal frequency, it must be admitted that the roentgenologic osseous changes seem comparatively frequent in the acute leukemia. That this conception has not been generally acknowledged is evidenced by a statement by Jean V. Cooke in 1938: »Examination of the extremities in which pain arises is usually negative and shows no characteristic roentgenological changes.»

The temperature shows no uniformity. However, except for in 3 cases, all the patients have for a shorter or longer period of time had a febrile period with rises in temperature up to more than 38°. 17 patients have had rises in temperature to above 39°. In none of these cases there was found a local cause for the fever.

The sedimentation reaction has been carried out in 18 cases, and has revealed values between 14 mm and 164 mm after 1 hour.

Blood culture has been made 4 times. 3 times there was no growth of bacteria, once of streptococci.

13 patients clinically show bleeding-tendency, petechias in the skin, minor bleedings in the oral cavity, major bleedings in skin, nose and intestines. In the present material no parallelism has been shown between the bleeding-tendency and the number of thrombocytes. Hemorrhages occur at thrombocyte values of 220 000, and the bleedings-tendency is not clinically present in a case of 34 000 thrombocytes per mm^3 .

In a separate case a specimen has been excised from a leukemic skininfiltrate. The pathologic-anatomical diagnosis pronounced was roundcell sarcoma, but this was revised when clinically one

arrived at the diagnosis of paramyeloblast leukemia. This one case confirms the experience that too great weight should not be put on the microscopic diagnosis in these cases, a condition that also has been emphasized by V. COOKE.

In 19 cases sternal puncture has been made. In 1 case the puncture was unsuccessful. In the remaining 18 cases there was every time found bone marrow rich in cells, and of an appearance corresponding to what is seen in myelogenous leukemia. The dominant cellular type was the myeloblasts, partly of the partly of the micromyeloblast type, and it was present in up to 99.4 %. In the remaining 6 cases the diagnosis has been made on basis of the clinical symptoms in connection with the blood-smear. In 3 cases the diagnosis of myeloblast leukemia has been pronounced, in 3 cases that of lymphatic leukemia. Totally the diagnosis of myeloblast leukemia has thus been made in 21 out of 24 cases.

In examination of the laboratory reports on the preparations, partly also in study of the very preparations, nothing has been found that creates doubt as to correctness of the diagnosis. But the diagnosis of *lymphatic* leukemia may possibly be questioned. It is well known that in these conditions the individual cellular form is not easily classified. Thus SCHULTEN believes that not even a hematologist is able to pronounce the diagnosis on basis of all these cells.

There is one striking phenomenon that recurs on examination of the blood-smear preparations in those cases in which also sternal puncture has been made. *Before* the sternal puncture there is in 17 of 18 cases found considerable lymphocytosis in the blood-smear preparations. *After* the sternal puncture this lymphocytosis is reduced, eventually has vanished completely, whereas on the other hand there are rich findings of various types of myeloblasts in the peripheral blood. It can hardly be doubted that on the first examination one is faced with an erroneous diagnosis, — the myeloblasts having been diagnosed as lymphocytes. Especially in the case of micromyeloblasts this error in diagnosis is quite comprehensible. This condition reduces the reliability of the diagnosis of *lymphatic* leukemia in cases in which sternal

puncture has not been made. In neither of the 3 cases of lymphatic leukemia from the present material has sternal puncture been carried out. In 2 of these cases section has been made, and also the pathologic-anatomical diagnosis has been *lymphatic leukemia*. That neither this last should be considered as conclusive is evident from the preceding. In the third case there has been no obduction.

As conclusion to these considerations it may be stated that the diagnosis of myelogenous leukemia has been made in 21 out of 24 cases of acute leukemia in children. In 3 cases the diagnosis has been lymphatic leukemia. This diagnosis may with good reason be questioned, as it has not at all been proved that also in these cases myelogenous leukemia is not involved. Symptomatically these three cases are no different from the remaining ones. The material tells in favour of the theory that the acute lymphatic leukemia in childhood is *rare*, if existing at all.

Concerning the comparative frequency of the myelogenous, respectively lymphatic acute leukemia in children, highly varying conceptions otherwise prevail, which should be read as an indication that a certain diagnosis not always is possible, and that the conceptions of morphology and extraction of the various cells have not been entirely clarified. From recent literature on acute leukemia in children it may be mentioned that Olof Brandberg in his material from various Swedish hospitals has found 82 cases of lymphatic leukemia, whereas myelogenous leukemia was represented in 29 cases. Too great importance should not be attributed to these proportional numbers, as the author strongly emphasises, because the morphologic diagnosis is difficult and one arrives »—in manchen Fällen im Zweifel darüber, um welche Form der Leukose es sich gehandelt hat».

E. & S. H. point out the relative lymphocytosis as a characteristic feature in the acute aleukemic myelogenous leukemias. The lymphocytosis has already been drawn to attention. (Ortner-Pinkus sign: lymphocytosis above 60 % = leukemia.) With children however, this symptom can be attributed no value whatsoever, as lymphocytosis up to the age of 14 years lies between 54 % and 75 %.

The red blood cells in the present material show nothing very special. However, in a few cases young forms have been found, partly as nucleuscontaining red blood cells. This is no unusual phenomenon in anemia in children.

Compared to E. & S. H.'s material this examination presents some features that are worthy of attention: On admission to the hospital there is in their material found splenic tumor in 5 out of 22 cases, large glandular tumor in 1 case only, moderate or small glandular tumor in 9 cases. In the present investigations the splenic and the glandular tumors are common symptoms at time of the patient's admittance to hospital, such that all patients but one offer both or one of these symptoms. It is possible that these symptoms are particularly frequent in earlier age — which also has been claimed by the said authors. There is possibly some connection between this phenomenon and the special «lymphatic» reactional mode of the child. The glandular tumor and the splenic enlargement are being considered as specially valuable symptoms in the early diagnosis of acute leukemia in childhood.

In the present material enlarged tonsils have been found 2 times, whereas in that of E. & S. H. it occurs 6 times.

The same authors find a connection between the number of thrombocytes and the bleeding-tendency. No doubt but that this result is in accordance with the general experience. The problem cannot be considered as solved, however. Authors like WILLI, COOKE, BRANDBERG and SCHULTEN do not confirm this theory. Neither does the present material support such conception. It should be kept in mind that the methods for determination of thrombocytes are not quite satisfactory. Toxic damage of the vascular wall or defect in the thrombocytes present («thrombopathy») may be thought responsible for the bleeding-tendency, which also has been claimed at various quarters.

SCHULTEN, NORDENSON et al. believe that various noxes, roentgen irradiation (as shown by GLOOR), tar (EMILE WEIL), operative interventions, infections are capable of releasing the acute myelogenous leukemia. This approaches a problem of pathogenesis of the disease at the widest, and cannot be discussed in the present.

Here only briefly it will be discussed the connection between the acute leukemia and eventual infections. Only twice in the present material have acute infections been observed in immediate connection with the initial stage of the disease. These numbers cannot be said to give any support to the theory of an infection releasing the acute leukemia. Even if infections frequently were seen in connection with the acute leukemia, this would be no proof of the pathogenetic significance of the infection. The possibility remains that the leukemic organism is specially susceptible to infections, partly because of the anemia and the generally reduced resistance, partly because the pathological white blood cells are not believed to offer any protection against the infection. (*«Blood-parasites»*: SCHULTEN). This latter hypothesis, that has been generally accepted, to a certain extent has been contradicted through examinations by BICKHARD. He found the identical pathological cellular forms in the inflammatory exudates of the patient as in his blood. JEAN V. COOKE finds no marked frequency of infections in his material, and he insists that during an infection it may be observed good reaction from the bone marrow with an increase in the number of pathological cells and a corresponding fall after the infection is over.

A phenomenon closely connected with these considerations is the question of the *leukemoid reactions*, Ward's »secondary or symptomatic reactions». Indeed, authors like FERRATA and STERNBERG believe that the acute leukemia (in contrast to the chronic form) is a response of the organism to a septic infection, and that there are all transitional forms between this one and the leukemoid reactions, as response to such infection. Thus they deny any essential difference between these two diseases. In fact, all acute leukemias should, according to their definition, be read as leukemoid reactions.

Several conditions that cannot be mentioned here are contradictory to such a conception. The leukemoid reactions should, from a pediatric point of view, temporarily be registered as one of the many strange, and in its nature unexplained reactional modes of the blood-forming organs of the child. That the diagnosis may be a difficult one appears from the following case:

A baby of 3 weeks was admitted to the Pediatric Department of the University Hospital in the autumn 1944, with an infected umbilical region, high fever, abscesses. The patient was treated with sulphathiazol 2.5 gms, and 2 days later the number of white blood cells was 2 400, and a severe granulocytopenia was found. Differential count of the peripheral blood revealed:

Myel.	Premyel.	Bas.	Eos.	N. myel.	Meta.	Band.	Polyn.	Mono.	Lymph.	Plasm
45	2		1	1	5	3	15		28	

However, the sternal and the tibial punctates gave no certain clues to the differential diagnosis of acute leukemia — leukemoid reaction. Abundant myeloblasts were found, it was not possible however with certainty to decide whether these were of *pathologic appearance*, such as is required by Naegeli in order to allow the diagnosis of leukemia. (Paramyeloblasts.)

In such a case one might with almost equal right claim the case to be a septicopyemia with leukemoid reaction and an acute leukemia of aleukemic type with secondary infection.

Summary.

Account of 24 cases of acute leukemia in children.

The acute leukemia in children as a rule is a myeloblast-leukemia (in at least 21 of 24 cases).

The initial symptoms are diffuse, — fatigue, fever, lack of appetite and pallor. In most cases (23 of 24) there is found either splenic or glandular enlargement and besides, in 13 cases also enlargement of the liver. These symptoms are considered as specially valuable in an early diagnosis.

3/4 of the cases commence in the first 5 years of life.

Anemia is a frequent symptom in an early stage of the disease, but in some cases it may be absent for weeks.

The red blood corpuscles show no characteristics. Index varies between 0.7 and 1.8. In 20 out of 23 cases index lies between 0.8 and 1.2.

Clinical bleeding-tendency is found in 50 % of the patients in the more advanced stages of the disease. No connection between the bleeding-tendency and the number of thrombocytes has been demonstrated.

The number of white blood cells varies within wide limits, from 1300 to 185 000 per mm^3 of blood. It also varies highly from time to time in the individual patient. On admission to the department, 21 of 24 patients show values below 20 000 white blood cells per mm^3 of blood, 17 below 10 000. 2 patients showed above 30 000 white blood cells per mm^3 of blood.

Roentgen picture of the bones have been taken in 17 patients. 5 show certain changes similar to those that sometimes are found in acute leukemia.

In 18 cases it has been made successful sternal puncture with findings of bone marrow rich in cells, with up to 99.4 % of myeloblasts. The pathological cellular type has in all cases been demonstrated in blood-smear preparations, in 17 of 18 cases however, they have been recognised as myeloblasts only after successful sternal puncture having ascertained the diagnosis.

References.

- BRANDBERG, O.: Acta Paediat. Vol. XXX. Suppl. I. 1943. — — —: 30/LL, 1942. — BRENNEMANN: Practice of Pediatrics 1938. — OLE K. EVENSEN & HALL SCHARTUM-HANSEN: Acta med. scand. Vol. CVII/III—V, 1941. — FINKELSTEIN, H.: Sänglingskrankheiten, 1938. — JOHANSSON, G. A. & WESTERGREN, A.: Nord. med. 13: 382, 1942. — LICHTENSTEIN, A.: Nordisk Lærebok i Paediatric. — MALMBERG, N.: Acta Paediat. 4: 410, 1925. — NORDENSON, N. G.: Lærobok i klinisk hæmatologi, 1944. — NAEGELI, O.: Blutkrankheiten und Blutdiagnostik, 1931. — SALOMONSEN, L.: Acta Paediat. 9: 497, 1930. — SCHULTEN, H.: Lehrbuch der klinischen Hämatologie, 1939.

Schönlein-Henochsche Purpura als Komplikation der Diphtherie-Schutzimpfung.

Von

HUGO JELKE.

Die Purpura ist das äusserlich sichtbare Zeichen einer gesteigerten Blutungsneigung, einer hämorrhagischen Diathese, gleichgültig, ob sich die Manifestationen auf die Haut beschränken oder auch noch Schleimhäute bzw. innere Organe in Mitleidenschaft ziehen. Eine derartige Diathese (oder, beim Fehlen hereditärer oder konstitutioneller Momente, »Scheindiathese«, MORAWITZ¹, CATEL²) kann sich auf verschiedenen Wegen etablieren, wobei die im wesentlichen wirksamen Faktoren folgende sind: a) eine abnorme zytologische Zusammensetzung des Blutes, wie bei gewissen anämischen Zuständen, Leukämie, Thrombopenie; b) eine mangelhafte Gerinnung des Blutes, z. B. bei Hämphilie, Hypoprothrombinämie infolge von Mangel an Vitamin K (Morbus haemorrhagicus neonatorum, Okklusionsikterus, Leberaffektionen), Afibrinogenämie, bzw. erworbene Fibrinopenie; c) eine gesteigerte Brüchigkeit der Gefässe, wie bei C-Avitaminose, bei septischen oder toxischen Schädigungen der Kapillaren (vgl. die »Bleiflecke« bei maligner Diphtherie) sowie bei toxisch-allergischer Beeinflussung dieser (Schönlein-Henochs anaphylaktoide Purpura). Auch die erhöhte Blutungsbereitschaft auf Grund von Mangel an dem noch strittigen Permeabilitätsvitamin P würde hierher gehören.

Man findet indessen im Einzelfalle oft ein Zusammenwirken der verschiedenen Faktoren, der Vitia sanguinis und der Vitia vasorum, wie VAHLQUIST³ den Sachverhalt ausdrückt. Es hat

nämlich den Anschein, als übe ein regelwidrig zusammengesetztes Blut einen deletären Einfluss auch auf das Kapillarendothel aus, was wohl die Voraussetzung dafür ist, dass überhaupt spontane Blutextravasate auftreten können.

Der Fall von Blutungsübel, über welchen ich hier berichten möchte, gehört in die letzte Gruppe, die mit vaskulärer Genese, und hat in Kürze folgende Krankengeschichte:

Die Patientin, ein 3jähriges Mädchen (geb. 17.7. 1941) wurde während der Zeit 20.9.—1.11. 1944 in der hiesigen Kinderabteilung unter der Diagnose *Purpura anaphylactica Schönlein-Henoch*, *Anaemia stationär* behandelt. Sie ist das zweite von 2 Geschwistern. Die Eltern sind gesund, ebenso die 4jährige Schwester, und eine erhöhte Blutungsneigung ist, soweit bekannt, niemals in der Verwandtschaft vorgekommen, ebensowenig wie allergische Affektionen oder »Arthritismus«. Das Kind wog bei der Geburt 3,9 kg, erhielt die Brust und entwickelte sich normal. Es bekam den ersten Zahn im Alter von 4 Monaten und konnte bald nach Vollendung des ersten Lebensjahres laufen. Bis auf Keuchhusten hatte es keine der gewöhnlichen Kinderkrankheiten gehabt und war früher stets gesund gewesen.

Am 8.9. 1944 wurde das Kind bei der öffentlichen Impfung in der Stadt gegen Diphtherie geimpft (1 ml Anatoxin subkutan interscapulär). Zwei Tage später wurde bemerkt, dass eine Anzahl bis dreimarkstückgrosse blaurote Flecke an den Beinen aufgetreten waren, und zwar sowohl an den Streck- wie an den Beugeseiten. Die Flecke waren etwas erhaben, fühlten sich ziemlich hart an und waren druckempfindlich. Am nächsten Tage wies das Kind ebensolche Flecke in der Glutäalregion auf beiden Seiten auf, so dass es infolge der Druckschmerzhaftigkeit nicht sitzen konnte. Die Temperatur ging nicht über $37,2-37,3^{\circ}$ hinaus. Nach 2—3 Tagen begannen die Flecke zurückzugehen, die Schwellung klang ab, und die Farbe ging in mehr blaue bis blaugraue Nuancen über. Das Kind wirkte aber nicht richtig gesund, es war etwas übelläunig und matt, und am 15.9., eine Woche nach der Impfung, bekam es eine *neue Aussaat* von Flecken, diesmal an den Armen, hauptsächlich an den Streckseiten. Diese Flecke hatten eine grellere rote Farbe, wurden aber allmählich immer mehr blau. Am folgenden Tage (16.9.) klagte das Kind über Bauchschmerzen, die stossweise auftraten, und hatte einmal Erbrechen. Am 18.9. wurde der Urin durch Blutbeimengung dunkelbraun, und es sollen sogar kleine Blutgerinnsel entleert worden sein; es bestanden jedoch keine Miktionsbeschwerden in Form von Brennen oder vermehrtem Harndrang. An demselben Tage wurde eine Anschwellung der Füße beobachtet; einen Tag später schwellen auch die Hände an und schmerzten, die Füße waren da blaufleckig.

Die Temperatur war während der ganzen Zeit nur leicht erhöht, 37,2—37,7°. — Der Appetit war an den letzten 4 Tagen vor der Aufnahme schlechter als sonst, und das Kind klagte ab und zu über Schmerzen in der Mitte des Leibes. Früher hatte es gut gegessen (gewöhnliche gemischte Kost). Keine Anhaltspunkte für Vitaminmangel. Auf Rat eines Arztes erhielt das Kind am 17. und 18.9. ein Abführmittel (Rad. glycyrrhic.); in der übrigen Zeit waren die Stühle wie gewöhnlich gewesen. — Sonst hatte das Kind keinerlei Arzneimittel bekommen. Am 18.9. wurde ein Arzt konsultiert, der ausser einer ziemlich allgemeinen Aussaat von Hautblutungen (s. Farbenphoto*) Eiweiss und Blut im Urin feststellte und das Kind in die Abteilung überwies.

Befund bei der Aufnahme am 20.9.1944: Allgemeinzustand nicht nennenswert beeinträchtigt. Temperatur 37,3°. Länge 107 cm, Gewicht 17,1 kg. Normal entwickeltes Kind, Psyche o. B. Allgemeine Hautfarbe ziemlich gut. Hände und Füsse sind geschwollen, namentlich der re. Handrücken ist stark ödematös, kissenförmig aufgetrieben, etwas druckempfindlich; nach Druck bleiben tiefe Gruben bestehen. Keine Lippenzyanose. In erster Linie fallen zahlreiche *Hautblutungen* auf: in der Umgebung des re. Ellbogens ein paar $3 \times 1\frac{1}{2}$ cm grosse sowie einige kleinere blauviolette Flecke, die auf Druck nicht verschwinden, distalwärts von diesen an der Dorsalseite des Unterarms 6 ähnliche Stellen, deren Durchmesser bis 1 cm beträgt. An den Fusssohlen mehrere bis bohnergrosse graublaue Flecke sowie eine Anzahl ähnliche rings um den li. Fussrand. Unterhalb des medialen Malleolus am li. Fuss einzelne punktförmige Petechien von blauroter Farbe. Am re. Fuss eine ziemlich dichte Aussaat von stecknadelkopfgrossen roten Petechien oberhalb des lateralen Malleolus und vor demselben. Schleimhautblutungen sind nicht zu sehen. Rachen blass, Tonsillen klein, Zähne und Zahnfleisch o. B. An beiden Kieferwinkeln fühlt man je eine erbsengrosse Lymphdrüse, eine ähnliche links am Nacken, mehrere reiskorngrosse an den Halsseiten. Lungen und Herz ohne krankhaften Befund, Blutdruck 105/60. Der Bauch erscheint leicht aufgetrieben, ist aber weich und nicht sicher druckempfindlich. An der rechten Bauchseite konstatiert man Flankendämpfung, die sich bei Lagewechsel verschiebt, auch Andeutung von Wellenschlagphänomen, aber irgendwelche Resistenzen sind nicht palpabel. Leber und Milz nicht tastbar. Reflexe normal. Facialisphänomen positiv (Chvostek I). Augenhintergrund beiderseits frei von Blutungen.

Der *Harn* war makroskopisch blutig, hatte aber schon am nächsten Tage die normale Farbe angenommen, und das Sediment war da o. B.; der Urin enthielt jedoch während der ganzen ersten Woche Eiweiss in geringen Mengen (bis 0,2 ‰).

* Herrn Dr. FAGERSTRÖM, der mir die Lichtbilder freundlichst zur Verfügung gestellt hat, spreche ich hier nochmals meinen aufrichtigen Dank aus.

Blut (21.9.). Hb. (nach SAHLI) 50 %, rote Blutkörperchen 3,32 Mill., weisse 6 800, davon Neutrophile Jugendformen 2 %, Stabkernige 13 %, Segmentkernige 48 %, Eosinophile 5 %, Lymphozyten 23 %, grosse Mononukleäre 9 %. Thrombozyten 378 000, kamen auch in der Folge in normaler oder ein wenig erhöhter Anzahl (496 000) vor, zeigten morphologisch keine Abweichungen, auch funktionell nicht, indem sie im Ausstrichpräparat normal agglutiniert lagen.

Gerinnselretraktion normal. Wa. R. und M. K. R. II negativ. Reststickstoff 34 mg%. SR 19; 29.9.: 2; 6.10.: 37; 13.10.: 20; 27.10.: 12 mm.

Faeces: okkulte Blutung (Benzidinprobe + + +) bis 11.10.

Hess'sche Probe (80 mm Hg 3 min): keine Petechien. 30.9.: 2 Petechien; 25.10.: 7 Petechien; 26.10. (50 mm Hg 15 min): 7 Petechien.

Intrakutane Tuberkulinprobe (1 mg) negativ.

Sonstige Untersuchungen:

21.9. Bestimmung der *Gerinnungszeit* nach HEDENIUS: 5 min 15 s. *Blutkalk* 8 mg%. 22.9. *Blutungszeit* (nach DUKE) 1 min 33 s (anfangs starke Blutung), bei einer späteren Gelegenheit 3 min. 27.9. *Prothrombinzeit* 25 s, Index 112. C-Vitaminausscheidung im Urin (Dichlorphenol-indophenol-Methode) 30.9.: 2; 1.10.: 1,5; 2.10.: 2,1 mg%. 30.9. *Plasmaeiweiss* 5,75 %, davon Albumin 2,92, Globulin 2,47, Fibrinogen 0,36% (med.-chem. Laboratorium des Karolinischen Krankenhauses). 9.10. *Blutkalk* 9,8 mg%, Blutphosphor 5,3 mg%. 30.10. *Plasmaeiweiss* 7,03 %, davon Albumin 4,68, Globulin 2,04, Fibrinogen 0,31%. 31.10. Hb. 58 %, rote Blutkörperchen 3,8 Mill.

Verlauf: Die Temperatur war in der ersten Woche leicht erhöht, 37,0—37,6° und gipfelte nach 10 Tagen mit 38°; während des übrigen Teils des Krankenhausaufenthalts war das Kind afebril. Schon am zweiten Tage nach der Aufnahme waren die Ödeme nahezu verschwunden und die Hautblutungen im Abblassen, wobei sie die Farbskala über Purpurbraun und Braun in immer weniger gesättigten Tönen bis zu Gelb durchliefen. Am dritten Tage nach der Aufnahme bekam das Kind recht schwere, in der Nabelgegend lokalisierte Bauchschmerzen, die es während der ganzen folgenden Nacht nicht ruhig schlafen liessen. Der Bauch war nach wie vor weich und unempfindlich. Gleichzeitig mit den Bauchsymptomen trat eine *neue Eruption* von Purpuraeffloreszenzen auf, und zwar in Gestalt linsengrosser, grellroter Flecke, die namentlich in der Glutäal- und Genitalzone, aber auch an der linken Hüfte sassen, wo indessen die einzelnen Flecke grösser, pfennigstückgross, und konfluierend waren. Zugleich schwell das li. Ellbogengelenk an, und auch die Lippen wurden etwas dick.

Den weiteren Verlauf kennzeichneten mehrere *Nachschübe* der Purpura, nämlich am 29.9., 4.10., 9.10. und 17.10., wobei aber Intensität und Ausdehnung jedesmal geringer wurden. In demselben Grade, wie also die Purpura an Intensität verlor, begannen die einzelnen Efflores-

zenzen in grösserem oder geringerem Umfang einen mehr urtikariellen Charakter anzunehmen, d. h. sie boten das Bild etwas erhabener Papeln mit einem weniger gesättigt-roten Farbton dar als die reinen Blutungen, blaskten jedoch nicht auf Druck ab; vereinzelte Effloreszenzen liessen Anzeichen eines Blutextravasats gänzlich vermissen. Die letzte Eruption vor der Entlassung war auf die Fussrücken beschränkt und rein petechial.

Die Behandlung war eine »antiallergische« mit Diät und Kalkpräparaten; daneben wurden C- und P-Vitamin in recht grossen Dosen (dreimal täglich 0,08 gr Ascorbinsäure) verabreicht. Vom 29.9. an wurden 2 Wochen lang dreimal täglich 0,25 g Azetylsalizylsäure gegeben, in der letzten Woche dreimal tägl. 0,025 g Ephedrin. Ausserdem bekam das Kind ein Eisenpräparat (Guttafer) sowie später Lebertran. Eine durchgreifendere Wirkung auf den Krankheitsverlauf hatte die Behandlung nicht, es folgte Schub auf Schub, einmal sogar unmittelbar nach intravenöser Injektion von 10 ml 10%iges Calcinat — allerdings wurden die Ausbrüche Schritt für Schritt schwächer.

Bei der Entlassung befand sich das Kind in einem guten Zustand, mit Ausnahme einer gewissen Anämie (Hb. 58 %), das Gewicht war um fast 1 kg auf 18 kg gestiegen, die Haut war bis auf eine schwache grau-braune Verfärbung an den Fussrücken, einen Rückstand der letzten Purpuraeruption, frei von Blutungen.

Schon am Tage nach der Ankunft zu Hause bekam das Kind aber einen neuen Schub von ein wenig erhabenen, roten Hauteffloreszenzen an den Füssen sowie vereinzelt auch an den Unterschenkeln. Es erhielt da dreimal täglich 1 Tablette Kalcodrin forte. Später war es gesund bis zum 12.11., wo es Fieber (bis 39,6°) und Schmerzen in den Beinen bekam; 3 Tage danach trat eine Aussaat von linsengrossen bläulichen Flecken an den Unterextremitäten auf. Es wurden nun 20 ml menschliches Serum intramuskulär injiziert, worauf es dem Kinde 3 Monate lang gut ging. Mitte Februar 1945 im Anschluss an eine Infektion der oberen Luftwege leichte Anschwellung der Kniegelenke mit Fieber bis 39,6°. Nach 3 Tagen bemerkte man wiederum eine Eruption von Hautblutungen an den Füssen und Unterschenkeln in Form von bis erbsengrossen rosaroten Flecken. Das Kind erhielt dreimal täglich 1 Tablette Kalcodrin und ist seitdem gesund gewesen.

Epikrise. Es handelt sich also um ein 3jähriges Mädchen, das 2 Tage nach der Diphtherie-Schutzimpfung Hautblutungen, am nächsten Tage Bauchschmerzen vom Koliktypus und danach auftretende Ödeme an Händen und Füssen, Empfindlichkeit der Handgelenke und schliesslich eine Nierenblutung bekam. Die Temperatur war nur leicht erhöht (bis 37,7°). *Objektiv* fand man

eine Anzahl von Hautblutungen, speziell an den Extremitäten, und zwar sowohl grössere Ekchymosen wie kleinere Petechien, Ödem der Gliederenden, Anzeichen von Nieren- und Darmblutungen sowie eine gewisse Sekundäranämie. Die übliche klinische Untersuchung des Blutes fiel sonst negativ aus, abgesehen von einer leichten Eosinophilie von 5—6 %, und was die Thrombozyten betrifft, denen bei jedem Blutungsleiden besonderes Interesse zukommt, so waren diese in normaler (oder sogar übernormaler) Anzahl vorhanden, und ihre Funktion, soweit sie sich in der Eigenagglutination und Gerinnselfretraktion zu erkennen gibt, war ebenfalls ganz normal. Blutungs- und Gerinnungszeit waren normal, und eine gesteigerte Brüchigkeit der Kapillaren liess sich weder bei supradiastolischem (BEXELIUS⁴) noch bei infradiastolischem Druck (GÖTHLIN⁵) nachweisen. Von sonstigen Untersuchungsergebnissen sei noch erwähnt: Normale Prothrombinzeit, aber etwas herabgesetztes Plasmaeiweiss, namentlich Verminderung der Albuminfraktion, so dass der Albumin-Globulinquotient etwas niedrig (1,2) war, eine Abweichung, die vor der Entlassung zum Ausgleich kam.

Die Nierenblutung hörte schon am Tage nach der Aufnahme auf, aber als Zeichen einer gewissen weiterbestehenden Reizung fand man während der ersten Woche ein wenig Eiweiss im Urin. Keine Anzeichen einer Niereninsuffizienz. Die okkulte Blutung aus dem Darm (Benzidinprobe + + +) hielt ganze 3 Wochen an, mit einem kurzdauernden Rezidiv nach zweiwöchiger Pause, das wahrscheinlich auf einen Provokationsversuch (s. unten) zurückzuführen ist. Neue Hautblutungen traten in fünf deutlich voneinander getrennten Schüben auf, wobei sie sukzessive immer schwächer wurden; zugleich machte sich an den einzelnen Effloreszenzen zum Teil ein urtikarieller Einschlag bemerkbar. Das mit Kalkpräparaten, Ephedrin, C- und P-Vitamin behandelte Kind wurde nach einem Krankenhausaufenthalt von 6 Wochen gebessert entlassen, bekam aber nach der Ankunft zu Hause drei weitere Eruptionen von Hautblutungen, die letzte im Anschluss an eine Infektion der oberen Luftwege reichlich 5 Monate nach dem Einsetzen der Erkrankung. Das Kind ist seitdem während der 1¹/₂jährigen Beobachtungszeit gesund gewesen.

Diagnose. Das hier beschriebene Bild deckt sich in jeder Beziehung mit demjenigen Krankheitszustand unter den hämorrhagischen Diathesen, welcher als Schönlein-Henochsche Purpura bekannt ist, und dessen Kardinalsymptome eben Hautblutungen, Ödeme und Gelenkerscheinungen, Darmkolikschmerzen mit Melaena sowie nicht selten Hämaturie sind. Irgendwelche speziellen Blutveränderungen, abgesehen von einer gewissen Eosinophilie und unter Umständen Sekundäranämie, brauchen bei diesem Zustand nicht vorzuliegen, und die Thrombozyten zeigen gewöhnlich weder quantitative noch qualitative Abweichungen. Die Gerinnselfretraktion ist normal, ebenso die Blutungs-, Gerinnungs- und Prothrombinzeit*; also alles Kriterien, die der vorstehend wiedergegebene Fall klar und eindeutig erfüllt. Typisch ist eine herabgesetzte Kapillarresistenz, die sich jedoch nicht immer demonstrieren lässt, wenigstens nicht mittels des Hessschen Verfahrens. Eine Ursache hierfür kann das verhältnismäßig häufige Vorkommen von Ödemen oder Präödemen sein, wodurch nach GÖTHLIN⁵ die Voraussetzungen für die Brauchbarkeit der Kapillarprobe in hohem Grade modifiziert werden. (AUBERTIN⁶ erwähnt 3 Fälle von Purpura, bei denen sich eine Brüchigkeit der Kapillaren nicht nachweisen liess, bei 2 Fällen sogar nicht, obgleich sich an dem zur Probe dienenden Arm spontan entstandene Petechien fanden. Er zieht den Schluss, die Purpura sei in diesen Fällen »fast rein hämatischen« Ursprungs — macht aber sonst nicht die geringsten hämatologischen Angaben.)

Irgendwelche Anhaltspunkte für C-Vitaminmangel gibt es bei unserem Fall nicht. Zahnfleischveränderungen fehlten gänzlich, und neue Purpuraschübe traten auf, obwohl der Organismus durch reichliche Zufuhr von Vitamin C ziemlich gesättigt gewesen sein dürfte; an mehreren Zeitpunkten konnte auch die Ausscheidung von Ascorbinsäure im Urin konstatiert werden.

* HOET und van VYVE⁷ behaupten jedoch, Hypoprothrombinämie bei der Schönlein-Henochschen Purpura beobachtet zu haben, und berichten sogar über günstige Erfahrungen mit K-Vitaminbehandlung bei diesem Zustand, ebenso wie SCHAAD⁷, der indessen nie den Prothrombingehalt bestimmte. Hiergegen kann angeführt werden, dass die Beurteilung eines Behandlungsergebnisses bei einem Zustand wie Morbus Schönlein-Henoch nicht ganz leicht ist, da spontane Remissionen ja zum Krankheitsbilde gehören.

JERSILD* beschreibt einen Fall von Schönlein-Henochscher Purpura mit achtjähriger Dauer, der mit C-Vitamin vergebens behandelt worden war, — dann aber bei parenteraler Zufuhr von *Citrin* abheilte. Während der fünfmonatigen Citrinbehandlung erhielt Pat. eine gänzlich askorbinfreie Diät, ohne dass die Symptome rezidierten, woraus der Autor folgert, dass die Schönlein-Henochsche Purpura auf einem P-Mangel beruhe. Diese These wird von unserem Falle nicht bekräftigt, der ja u. a. auch Vitamin P erhielt, ohne wahrnehmbare Einwirkung auf dem Krankheitsverlauf. Hin und wieder können hormonale Störungen (wie in der Pubertät, im Prämenstruum), Ernährungsstörungen (Inanition) sowie gewisse Vergiftungen (Anilin, Nitrobenzol) zu einer gesteigerten Blutungsneigung Anlass geben, aber hierfür besteht keinerlei Beleg.

SEIDLMAYER¹⁰ hat viel Mühe und Scharfsinn darauf verwendet, eine besondere Purpuraform, die »frühinfantile, postinfektiöse Kokarden-Purpura« der Säuglinge und Kleinkinder von der eigentlichen Schönlein-Henochschen Purpura abzugrenzen. Als Begründung führt er dabei an, dass die Erkrankung in einem Alter auftrete, in dem der typische Morbus Schönlein-Henoch äussert selten sei, wenn er überhaupt vorkomme (FINKELSTEIN¹¹ bezeichnet einen Fall bei einem Säugling als Seltenheit), ferner ein obligat-postinfektiöses Auftreten sowie schliesslich das typische Aussehen der Purpuraeffloreszenzen mit einer erhabenen hellen Zone rings um den eigentlichen Bluterguss, so dass sich das Bild einer Kokarde ergibt. In seinem Material von 10 Fällen soll die Erkrankung bei 9 im Anschluss an Influenza, bei 1 bei Tbc. pulmon. ausgebrochen sein. Sie spielt sich in verhältnismässig kurzer Zeit mit 1—3 Schüben während höchstens 2 Wochen ab. Ödeme sind häufig, aber Gelenkschwellungen, Darmkolikschmerzen und Hämaturie kommen nicht vor. Hämatologisch wird mitunter eine gewisse Labilität des Thrombozytenwerts, sonst aber nichts Charakteristisches festgestellt. Ein Punkt, den SEIDLMAYER besonders betont, ist das Fehlen einer erblichen Belastung für »Arthritismus« und exsudative Diathese, und zwar im Gegensatz zu dem, was bei der eigentlichen Schönlein-Henochschen Krankheit der Fall sein soll. In einem aus 16

Fällen der letzteren Erkrankung bestehenden Material hat dieser Autor eine hundertprozentige Belastung nachgewiesen — wobei jedoch ein Fall von beispielsweise Polyarthrit, Herzfehler, Steinleiden oder Migräne bei Geschwistern oder in der Aszendenz als hinreichend erachtet wurde, um das Individuum als erblich belastet zu stempeln.

GLANZMANN¹² hat unter der Bezeichnung »postinfektiöse anaphylaktoide Purpura« von der eigentlichen Schönlein-Henochschen Purpura eine Sondergruppe von Fällen abgetrennt, nämlich solche, bei denen der Erkrankung eine Infektion vorangegangen war. Er teilt allerdings auf eine Anfrage SEIDLMAYERS mit, dass er solche Fälle niemals in einem so frühen Lebensalter beobachtet habe, wie es von der Kokarden-Purpura bevorzugt wird. Ein anderer von GLANZMANN¹³ unter der Diagnose Purpura fulminans veröffentlichter Fall bei einem 6 1/2 Monate alten Kinde, welches gesund wurde, scheint dagegen Berührungspunkte mit der SEIDLMAYERSchen Purpuraform zu besitzen.

Ob dieser letzteren wirklich die Dignität einer selbständigen Erkrankung zuzuerkennen ist, oder ob sie nicht eher als eine Variante der anaphylaktoiden Purpura Schönlein-Henoch aufzufassen wäre, durch für die betreffende Altersgruppe charakteristische konstitutionelle Verhältnisse bedingt, darüber könnte man vielleicht streiten. In dem oben beschriebenen Fall, wo es sich um ein 3jähriges Kind handelte, hatte die Erkrankung den die klassische Schönlein-Henochsche Purpura kennzeichnenden protrahierten Verlauf mit, neben Kolikschmerzen, Melaena und Hämaturie, 8 Schüben von Hauteruptionen im Laufe von 5 Monaten. Eine erbliche Belastung für »Arthritismus« liess sich nicht eruieren; mindestens *ein* Schub trat in unmittelbarem Anschluss an eine akute Infektion auf.

Kommentar. Der erste, welcher diese Purpuraform beschrieb, war SCHÖNLEIN, der in seinen Vorlesungen an der Charité vor 100 Jahren die Krankheit dem Morbus maculosus Werlhofii gegenüber abgegrenzt, auf die häufige Kombination von Hautblutungen mit Erythem hingewiesen, das Vorkommen einer Hämorrhoe aber bestritten hat (zit. n. BERGGREEN¹⁴). Man hatte frühzeitig erkannt, dass rheumatische Beschwerden bei jener Erkrankung ein gewöhnliches Symptom waren,

und ihr deshalb den Namen *Peliosis rheumatica* gegeben. HENOCH¹⁵ schilderte als erster im Jahre 1874 das gleichzeitige Auftreten von Hautpurpura und viszeralen Erscheinungen. Je nach dem vorherrschenden Symptom erhielt das Leiden verschiedene Bezeichnungen, wie *Purpura simplex*, *Purpura rheumatica*, *Purpura abdominalis*, eine Einteilung, der man noch in *Nordisk lärobok i intern medicin*, 1. Aufl., 1919, begegnet. Schon 1890 machten indessen DUSCH und HOCHÉ¹⁶ darauf aufmerksam, dass diese verschiedenen »Krankheiten« nur anders erscheinende Äusserungen ein und desselben krankhaften Zustandes wären, und seitdem hat sich der Name Schönlein-Henochsche *Purpura* allmählich durchgesetzt. FRANK¹⁷ prägte 1915 den Ausdruck *anaphylaktoide Purpura*, den sich im nächsten Jahre auch GLANZMANN¹⁸ zu eigen machte. Die Krankheit ist von dem ersteren Autor unter der Bezeichnung hämorrhagische Kapillartoxikose in Schittenhelms Handbuch des Blutes und der blutbildenden Organe besprochen worden.

Die Schönlein-Henochsche *Purpura* ist keine häufige Erkrankung. BERGGREEN¹⁴ fand unter 50 000 Patienten in der Hautpoliklinik der Berliner Charité bloss 28 Fälle, wobei er allerdings darauf aufmerksam macht, dass es nur eine Auslese hauptsächlich leichter, »abortiver« Fälle (*Purpura simplex*) sei, welche der Dermatologe zu Gesicht bekommt. Die Krankheit tritt vor allem bei Kindern und Jugendlichen auf; SEIDLMAYERS¹⁹ 16 Fälle z. B. befanden sich alle im Alter von 6 bis 20 Jahre. Die Erkrankung setzt meistens mit Hautblutungen an den Unterextremitäten ein, im weiteren Verlauf aber erscheinen neue Blutungen mehr über die Körperoberfläche verstreut. BERGGREEN gibt an, dass Fusssohlen und Fussränder frei bleiben — was indessen für unseren Fall durchaus nicht zutrifft. Bei einem der SEIDLMAYERSCHEN¹⁰ Fälle von Kokarden-Purpura ist auch das Befallensein der Fusssohlen ausdrücklich erwähnt, desgleichen bei einem Fall von LI. Die *Purpura* kann in einem einzigen Schub auftreten, der binnen 1—2 Wochen abblasst, aber typisch ist die Aufeinanderfolge mehrerer, gegeneinander gut abgegrenzter Schübe während eines Zeitraums von Monaten bis Jahre, bei einem von SEIDLMAYERS Fällen bis zu 1 1/2 Jahren, bei JERSILDS⁹ sogar bis zu 8. Hierbei nehmen die einzelnen Effloreszenzen oft einen mehr oder weniger urtikariellen Charakter an, und das Exanthem kann infolgedessen ein ziemlich buntes Aussehen bekommen. Stärkeres Jucken pflegt nicht vorhanden zu sein.

Zugleich mit der *Purpura* stellen sich oft Schmerzen und Empfindlichkeit der Gelenke mit oder ohne Anschwellung derselben ein, ausserdem sind Ödeme, namentlich an Händen und Füßen, etwas Häufiges. Hierzu gesellen sich in gewissen Fällen Bauchsymptome in Form von heftigen, kolikartigen Schmerzen in der Nabelgegend, manchmal mit Erbrechen. Die Deutung dieser Symptome macht im allgemeinen bei Vorhandensein einer *Purpura* oder anderer Anzeichen der Schönlein-

Henochschen Krankheit keine grösseren Schwierigkeiten; immerhin sei darauf hingewiesen, dass eine Invagination ab und zu einmal auch bei diesem Zustand beobachtet worden ist (SCHWARTZMANN).²⁰ Anders ist es, wenn die Erkrankung, wie es hin und wieder der Fall ist, mit Bauchsymptomen beginnt. Dass die Diagnose in derartigen Fällen beim Fehlen von mehr unmittelbar festzustellenden allergischen Erscheinungen leicht abwegig wird, versteht sich von selbst. ALTHAUSEN, DEAMER und KERR²¹ haben unter der Bezeichnung »the false acute abdomen« über etliche solche Fälle berichtet. BARNES und DUNCAN²² haben einen Fall von anaphylaktoider Purpura bei einem 30jährigen Mann beschrieben, bei dem das Bild dem einer subakuten Appendizitis bzw. Ileitis überaus ähnlich war, und wo die Hauterscheinungen ganz geringfügig waren. Bei der Operation fand man den distalen Teil des Ileum stark geschwollen, hyperämisch und ödematös mit subserösen Blutungen. Am nächsten Tage wurde die HESS'sche Probe angestellt, die positiv war. Pat. bekam eine Bronchitis, und infolge heftiger Hustenstösse öffnete sich am 9. Tage nach der Operation die Bauchwunde wieder, wodurch man in die Lage versetzt wurde, den Darm von neuem untersuchen zu können, der dann völlig normal aussah.

Man sieht ohne weiteres ein, dass eine derartige Veränderung im Darm leicht eine Enterorrhagie entstehen lassen kann, und es lassen sich auch in der Tat bei Fällen mit ausgeprägteren Bauchsymptomen ziemlich regelmässig Blutungen nachweisen, entweder okkulte oder solche in Form von Melaena. HAMPTON²³ hat einen Fall von Morbus Schönlein-Henoch bei einem 15jährigen Mädchen infolge einer Nahrungsmittelallergie mit bis 40 blutigen Stühlen in 24 Stunden veröffentlicht. Bei diesem Falle wurden auch zahlreiche eosinophile Zellen in den Faeces gefunden.

Die Nieren werden nicht selten von dem anaphylaktoiden Prozess in Mitleidenschaft gezogen, was sich als Hämaturie bei im allgemeinen unbeeinträchtigter Nierenfunktion zu erkennen gibt. KERN²⁴ berichtete aber in einer Diskussionsbemerkung über einen Fall von Nahrungsmittelallergie (gegen Rotzwiebel), bei dem die Anfälle der klassischen Haut- und Bauchsymptome von Hämaturie und selbst Azotämie (Reststickstoff über 100 mg%) begleitet wurden. Eine Attacke führte zum Tode an Urämie. Schleimhautblutungen, z. B. in Form von Nasenbluten, sind seltener; solches kam jedoch bei dem obenerwähnten HAMPTON'schen Fall von Nahrungsmittelallergie sowie bei LIS²⁵ zweitem Fall bei einem 8jährigen Knaben vor. Fieber kann vorhanden sein, insbesondere bei postinfektiösen Fällen, fehlt aber häufig.

Das Blutbild bietet, abgesehen von einer leichten Eosinophilie, nichts Charakteristisches. Der höchste Wert ist, soweit ich finden konnte, von HAMPTON mit 14 % festgestellt worden; bei unserem Falle ist höchstens 6 % verzeichnet. Dass sich mitunter eine gewisse Se-

kundäranämie entwickelt, liegt in der Natur der Sache. Die Thrombozytenzahl ist in der Mehrzahl der Fälle normal. Nicht selten bemerkt man im Laufe der Erkrankung einen mehr oder minder erheblichen Anstieg der Thrombozytenkurve, bei unserem Fall beispielsweise auf 496 000, möglicherweise ein Ausdruck für den anaphylaktischen Charakter des Leidens. SEIDLMEYER¹⁰ gibt für seine Kokarden-Purpura eine gewisse Labilität des Thrombozytenwerts an, bei 2 Fällen (vor 10) bestand sogar eine ausgeprägte Thrombopenie (bis 28 700), auf die indessen schon nach wenigen Tagen eine normale Thrombozytenzahl folgte.

Einer solchen transitorischen Thrombopenie begegnet man oft bei Purpura infolge von Überempfindlichkeit gegen gewisse Arzneimittel, z. B. Chinin (MARITSCHKE und MARKOWICZ²⁶ 1933), sowie namentlich Sedormid (LOEWY²⁷ 1934, FALCONER und SCHUMACHER²⁸, MEULENGRACHT²⁹, THIELE³⁰) und Sanocrysin (HEINILD³¹). Bei einem der Fälle von THIELE³⁰ nach Gebrauch von Saridon, das u. a. Sedormid enthält, schienen Thrombozyten zunächst gänzlich zu fehlen. Das Auftreten einer solchen Purpura mit Thrombopenie braucht keineswegs an Beziehungen zum Morbus maculosus Werlhofi denken zu lassen. Es ist nämlich typisch, dass die Erscheinungen rasch abklingen, und dass auch die Thrombozyten bald zur Norm zurückkehren, sobald das betreffende Mittel ausgesetzt worden ist. Bei diesen Fällen handelt es sich mehr um eine Verteilungsthrombopenie, indem sich die Thrombozyten in inneren Organen und Gefäßgebieten (in erster Linie im Splanchnicusgebiet) ansammeln dürften, wie es beim Peptonshock der Fall ist. HEINILD³¹ klassifiziert demgemäss diese Form von Thrombopenie als dysvaskulär-allergische im Gegensatz zur dyshämatopoetischen, und will damit zum Ausdruck bringen, dass die Thrombopenie hier nicht die Ursache der hämorrhagischen Diathese sondern die Folge einer allergisch bedingten Kapillarschädigung ist. Man kann nämlich bei diesen Fällen nicht, wie HEINILD sagt, irgendeine systematisierte Schädigung des hämatopoetischen Apparats nachweisen, d. h. irgendwelche Anhaltspunkte dafür, dass die Thrombopenie myelogen (oder, nach HEINILDS Einteilung, dyshämatopoetisch) verursacht wäre, bestehen nicht. Bei 3 Fällen mit reaktivem Symptomkomplex bei Sanocrysinbehandlung, der sich in Thrombopenie und hämorrhagischer Diathese äusserte, untersuchte HEINILD das Knochenmark, ohne andere Veränderungen als eine Eosinophilie zu finden. Bei dem von HAMPTON²³ beobachteten Fall, einem 15jährigen Mädchen mit Nahrungsmittelallergie, ergab die Sternalpunktion eine »Vermehrung der reifen und unreifen eosinophilen Zellen«, während THIELE³⁰ bei seinem Fall von Purpura nach Saridon einen völligen Mangel an Thrombozyten konstatierte (ebenso wie im Blut). Mehr Angaben über Knochenmarkuntersuchung bei der Schönleihenochschen Purpura waren in dem mir zur Verfügung stehenden

Schrifttum nicht zu entdecken (und die diesbezügliche Untersuchung ist auch bei unserem Falle nicht vorgenommen worden).

Die Gerinnungszeit ist normal, desgleichen gewöhnlich die Blutungszeit. In den Fällen, wo eine hochgradigere Thrombopenie vorliegt, ist indessen die Blutungszeit verlängert, was ja auch nicht anders zu erwarten ist; so überstieg sie bei dem erwähnten THIELESchen Fall 1 Stunde, bei MEULENGRACHTS²⁹ Fall von Sedormidpurpura 15 Minuten, während sie bei HAMPTONS²³ Fall von Nahrungsmittelallergie 17 Minuten betrug. Die Senkungsreaktion ist, wie BERGGREEN¹⁴ angegeben hat, oft erhöht, und so verhielt es sich auch bei unserem oben dargestellten Fall. Hierin liegt nicht notwendigerweise ein Hinweis auf eine Infektion, da die Senkungsgeschwindigkeit auch von derjenigen Reaktion beeinflusst wird, welche die parenterale Zufuhr artfremden Eiweisses (z. B. Milchinjektionen) im Organismus auslöst. Auch eine gleichzeitige reaktive Thrombozyten- und Leukozytenzunahme mit Linksverschiebung kann dabei hervorgerufen werden, worauf u. a. HEINILD³¹ aufmerksam gemacht hat.

Wie erwähnt bestand bei unserem Fall eine gewisse Hypoproteinämie infolge einer Verminderung der Albuminfraktion. Womöglich kann diese Erscheinung der gleichzeitigen Nierenreizung zur Last zu legen sein. Dass sie für die Genese der Purpura belanglos sein dürfte, geht schon daraus hervor, dass auch nach dem Anstieg des Plasmaeiweisses auf die Normalhöhe fortwährend neue Purpuraschübe auftraten. Eine Untersuchung des Plasmaeiweisses bei der Schönlein-Henochschen Purpura habe ich im Schrifttum nicht gefunden, bis auf einen von BING mitgeteilten Fall von Purpura abdominalis bei einem 40jährigen Manne, bei dem ein auffallend hoher Globulingehalt (7 %) konstatiert worden war (zit. n. WALDENSTRÖM³²). Der Gedanke, dass das Plasmaeiweiss jedoch in irgendeiner Beziehung zur Purpura stehen könnte, wurde von WALDENSTRÖM³² mit Rücksicht auf 3 Fälle von hartnäckiger Purpura unklarer Genese mit andauernd hoher SR geäußert; diese Fälle hatten alle eine Hyperglobulinämie (von 4,7—5,7 %; einer derselben wies jedoch gleichzeitig Anzeichen einer Lymphogranulomatosis benigna auf).

Wie bereits gesagt treten die Purpuraeruptionen gewöhnlich in mehreren Schüben über einen ziemlich langen Zeitraum hin auf; sie klingen aber, wie auch die übrigen Symptome, nach und nach ab, und die Prognose ist im grossen und ganzen gut. Fasst man indessen, wie GLANZMANN¹³, die Purpura fulminans als die schwerste Form der anaphylaktoiden Purpura auf, so wird die Vorhersage wesentlich getrübt, da ja diese Fälle in der Mehrzahl einen äusserst foudroyanten Verlauf haben. Dass viele dieser als Purpura fulminans beschriebenen Erkrankungsfälle in Wirklichkeit von einer Meningokokkensepsis, unter Umständen mit Blutungen in das Nebennierengewebe, verursacht worden sind, ist nach Massgabe unserer heutigen Erfahrungen auf diesem

Gebiet recht wahrscheinlich. Auch bei Fällen mit stürmischeren Bauchsymptomen ist es hin und wieder einmal zum tödlichen Ausgang gekommen. Der Russe WASSILIEFF³³ hat einen Fall von Morbus Schönleini-Henoch bei einem 21jährigen Mann mit u. a. Haematemesis und Meläna beschrieben, der 8 Tage nach Beginn der Erkrankung zum Tode führte — und bei dem die Obduktion multiple Geschwüre im Magen und Dünndarm ergab, die oft tief in die Muscularis hinabreichten, sowie ferner eine serös-hämorrhagische Peritonitis. Ein entsprechender Fall ist von RAMB³⁴ veröffentlicht worden. Ein chinesischer Autor, RYANG³⁵, berichtete über den Fall eines 13jährigen koreanischen Knaben, der angeblich an Henochscher Purpura ad exitum gekommen sein soll. Bei der Obduktion fand man hier vor allem eine Atrophie der Schilddrüse und der Nebennieren, sowohl der Rinde wie des Marks, während das interstitielle Gewebe gewuchert war. KERN²⁴ erwähnte einen Fall, der zur Gruppe der Nahrungsmittelallergien gehörte; der Tod erfolgte bei diesem im Anschluss an eine Attacke am ehesten durch Urämie.

Die anatomische Unterlage der Krankheit ist bis vor kurzem wenig bekannt gewesen, was damit zusammenhängt, dass so wenige Fälle zur Obduktion gelangt sind, und das gleiche gilt für die Pathogenese. Ein Umstand, der seinen Eindruck wohl auf keinen Leser der Schilderungen des Krankheitsbildes verfehlt, und der schon von FRANK¹⁷ und GLANZMANN¹⁸ hervorgehoben worden war, ist die unverkennbare Ähnlichkeit der Symptome mit denjenigen bei einer anaphylaktischen Reaktion, wie wir ihr beispielsweise bei der Serumkrankheit begegnen. Da bei experimentell erzeugter Anaphylaxie im allgemeinen keine Purpura zu entstehen pflegt, und da sich schlüssige Beweise für die Auffassung der Erkrankung als allergisch bedingt nicht erbringen liessen, haben jene Autoren den Ausdruck anaphylaktoide Purpura eingeführt. In späteren Arbeiten behandelte FRANK den einschlägigen Krankheitszustand eingehend unter der Bezeichnung »hämorrhagische Capillartoxikose«. Dass das pathologisch-anatomische Substrat der Erkrankung auch wirklich allem Anschein nach in den Kapillaren zu suchen ist, dafür sprechen die wenigen bisher vorliegenden histologischen Untersuchungen. So fand WASSILIEFF³³ bei seinem sorgfältig untersuchten Fall im Bereich der Hauteffloreszenzen stellenweise in den Kapillaren und Arterioli eine hochgradige Endothelwucherung, die geradezu in einer völligen Obturation der Lumina durch Endotheltromben gipfeln konnte. Die Magengeschwüre hatten nekrotische Ränder, die zuführenden Gefässe ein gequollenes, teilweise gewuchertes Endothel, die Media war fibrinoidartig-nekrotisch und das Lumen durch fibrinartige Thromben verschlossen. Auch in den Darmgeschwüren wurden Thromb-arteriitiden und hyaline Kapillarthromben konstatiert. — Es sind solche Gefässveränderungen, welche heutzutage als allergisch-hyperergisch bedingt aufgefasst werden, und WASSILIEFF betont, dass sie als die funda-

mentale Ursache der Gewebsalteration und damit der schweren Krankheitssymptome bei seinem Fall zu gelten hätten. Ähnliche Befunde (Endothelwucherung und Austritt neutrophiler Leukozyten rings um die Lymphbahnen), allerdings durchaus nicht desselben Schweregrades, erhob der dänische Forscher HEINILD⁴² durch Hautbiopsie bei einem Fall von Schönlein-Henochscher Purpura bei einem 5jährigen Knaben.

Spezielles Interesse in diesem Zusammenhang besitzt, dass sich durch eine allergische Reaktion ganz analoge Veränderungen experimentell bei Versuchstieren hervorrufen lassen. Nach dem heutigen Stande der Allergielehre (KLINGE, RÖSSLE, zit. n. HEINILD⁴¹, HAAG³⁸) liegt der allergischen Reaktion stets eine Antigen-Antikörperreaktion zugrunde. Nachdem ein Antigen, hier also Allergen, während einer gewissen Zeit auf den Organismus eingewirkt hat, reagiert dieser mit einer Antikörperbildung, die sich vorzugsweise in den Zellen des retikulo-endothelialen Systems abspielt. Von dort aus werden Antikörper in das Blut und die Gewebsflüssigkeit ausgeschwemmt, sie können an andere Körperzellen gebunden werden, und der Organismus ist »sensibilisiert«. Eine erneute Zufuhr des betreffenden Allergens bewirkt nun eine Antigen-Antikörperreaktion, einen Vorgang, der aus zwei Phasen besteht. Die erste ist die spezifische, aber nicht wahrnehmbare Verbindung zwischen Antigen und Antikörper, die an den Zelloberflächen des retikulo-endothelialen Systems sowie im Gefäß- und Bindegewebsapparat vonstatten geht. Hierdurch wird Histamin frei gemacht (ACKERMANN, zit. n. HAAG³⁸), durch dessen Wirkung auf Parasympathicus möglicherweise via Acetylcholin die zweite Phase ausgelöst wird. Dieser entspricht die unspezifische, äußerlich bemerkbare klinische Reaktion, bei der es sich um Spasmen der glatten Muskulatur, Shockwirkung auf die Gefäße usw. handeln kann, mit dann folgendem allgemeinem Shockzustand, örtlichen Ödemen u. a. m. Histopathogenetisch findet man dabei hauptsächlich im Endothel der Blut- und Lymphgefäße lokalisierte Veränderungen in Form von Endothelablösung, herdförmiger, degenerativer Anschwellung der Gefäßwände, »Verquellung«, Austritt von Plasma in die Gefäßwandung hinein oder durch sie hindurch in das umgebende Gewebe, perivaskuläre Leukozyteninfiltration mit reichlichem Vorkommen eosinophiler Zellen; mithin Veränderungen, die grundsätzlich mit denjenigen übereinstimmen, welche man bei den wenigen bisher histologisch untersuchten Fällen von Morbus Schönlein-Henoch festgestellt hat.

Haben wir somit pathologisch-anatomische Kriterien für den allergischen Charakter der Krankheit, so stehen heutzutage auch schlüssige klinische Beweise nicht mehr aus. Im Jahre 1941 gelang es LI²⁵ (an der Kölner Universitäts-Kinderklinik), bei 2 (von 4) Patienten, die vor kurzem eine Schönlein-Henochsche Purpura durchgemacht hatten, durch intravenöse Injektion von Purpurarekonvaleszentenserum (85—

120 cm³) Purpurarezidive mit Hämaturie (und in einem Fall auch Darmblutung) zu provozieren. LI weist darauf hin, dass Voss die analogen Verhältnisse bei der Serumkrankheit besonders studiert hat. Bei Kindern, die zuvor Pferdeserum erhalten hatten, liess sich durch intravenöse Einspritzung von Serumkrankheitsrekonvaleszenten Serum mit grosser Regelmässigkeit eine Serumkrankheit auslösen (sog. inverse Anaphylaxie). In beiden Fällen werden spezifische Antikörper zugeführt; während aber im letzteren das Antigen bekannt ist, wissen wir bei den Purpurafällen nichts darüber, mit welchem Allergen im Organismus sie reagieren.

Wenn es also nunmehr gerechtfertigt erscheint, die Schönlein-Henochsche Purpura als anaphylaktisch (LI) anstatt anaphylaktoid zu rubrizieren, ist doch damit noch nicht gesagt, dass sich das Allergen im Einzelfalle immer nachweisen lässt. Die Hautproben sind alles andere als zuverlässig. Es ist einerseits nicht sicher, dass die Haut auf ein Allergen reagiert, obwohl andere Gewebe dies tun, und andererseits braucht sich ein positiver Ausfall nicht notwendigerweise auf den aktuellen Zustand zu beziehen, sondern kann durch eine frühere Allergisierung verursacht sein. In einer derartigen Situation sind zur Sicherung der Diagnose Provokationsversuche mit der verdächtigen Substanz angezeigt.

In den letzten Jahren sind, namentlich von amerikanischer Seite, mehrere Fälle von Schönlein-Henochscher Purpura infolge von Nahrungsmittelallergie bekanntgegeben worden. (DUKE³⁷, ALEXANDER und EYERMAN³⁸, SQUIER und MADISON³⁹, LANDSBERGER⁴⁰, HAMPTON²³, KERN²⁴.)

Eine andere Gruppe von Fällen, bei denen das auslösende Allergen leicht in die Augen fällt, bilden die freilich sehr seltenen Erkrankungen an Schönlein-Henochscher Purpura im Anschluss an die Pockenimpfung. Soweit ich finden konnte, handelte es sich dabei immer um eine Erstimpfung. HEATON⁴¹ berichtete über einen 23jährigen Soldaten, der 14 Tage nach der Pockenimpfung an einer allgemeinen Aussaat von Hautblutungen, Blutung aus dem Zahnfleisch, Hämaturie und Teerstühlen erkrankte. Er hatte kein Fieber. Die eosinophilen Zellen im Blut sollen vermehrt, die Thrombozyten vermindert gewesen sein (zahlenmässige Angaben sucht man aber vergebens). Der Fall, der als eine thrombozytopenische Purpura, sekundär zur Impfung, aufgefasst wurde, hatte einen glücklichen Ausgang. Der Autor hat 7 andere Fälle aus dem Schrifttum angeführt, bei denen nach der Impfung eine Purpura auftrat, unter diesen einen Fall bei einem Individuum, das vorher mehrere Anfälle von Purpura gehabt hatte; bei wenigstens einem Fall bestand eine Thrombopenie. Ein derartiger Fall wird auch von REGAMEY⁴³ im Anschluss an *Vaccina generalisata* erwähnt. WEINGÄRTNER⁴⁴ sah bei einem 9 Monate alten Kind, das auch eine Hyperthrombozytose (756 800)

aufwies, 12 Tage nach der Impfung eine ziemlich ausgedehnte Purpura sowie Anschwellung der Hand- und Fussgelenke auftreten. Die Hautblutungen verschwanden ohne jede Therapie binnen weniger Tage (dieser Autor erwähnt, dass LENTZ und GINS in ihrem Handbuch der Pockenbekämpfung und Impfung, Berlin 1927, 4 ähnliche Fälle aus dem Schrifttum anführen). Ein typischer Fall von Schönlein-Henochscher Purpura nach Pockenschutzimpfung ist auch von HEINILD⁴² veröffentlicht worden. Es handelte sich um einen 5 1/2-jährigen Knaben, welcher 1 Woche nach der Impfung hohes Fieber bekam, das 3 Tage anhielt. Ein paar Tage später Eruption von »roten Pocken«, d. h. Purpuraeffloreszenzen, an den Extremitäten, dann Bauchschmerzen vom Koliktypus sowie Schmerzen in den Ellbogen- und Kniegelenken. Die Kapillarresistenz war herabgesetzt, und das Elektrokardiogramm machte Anzeichen einer vorübergehenden Myokardaffektion ersichtlich. Pat. wurde nach 4 Monaten geheilt entlassen.

Die Purpura im Anschluss an Pockenschutzimpfung scheint in der Mehrzahl der Fälle 10—14 Tage nach der Impfung aufzutreten zu sein, d. h. an einem Zeitpunkt, wo die spezifische Antikörperbildung ihren Höhepunkt erreicht hatte. Die Voraussetzung für eine besonders intensive Antigen-Antikörperreaktion wäre damit gegeben, und die entstandenen Reaktionsprodukte, oder vielleicht richtiger das frei gemachte Histamin, würden dann durch ihre toxische Einwirkung auf das Kapillarendothel die Krankheitserscheinungen hervorrufen. Wie soll man sich aber, falls dies zutrifft, die extreme Seltenheit der Erkrankung nach der Impfung erklären? Es finden ja jährlich Millionen und aber Millionen von Impfungen statt, und doch liegen bisher in dem gesammelten Schrifttum nur etwa 15 Berichte über Komplikation durch Morbus Schönlein-Henoch vor. Es ist jedoch zu betonen, dass das postvakzinale Exanthem, welches auch als eine allergische Reaktion auf artfremdes Eiweiss aufgefasst werden muss, allerdings viel leichteren Charakters, nicht ganz selten vorkommt. Die Annahme der Beteiligung eines *zweiten* Faktors bei der Pathogenese der Schönlein-Henochschen Krankheit nach der Pockenschutzimpfung dürfte jedoch kaum zu umgehen sein. Man muss an eine spezielle Reaktionsbereitschaft der Gefässwandung denken, mag diese nun auf konstitutionelle Momente besonderer Art oder auf eine vorübergehende Umstimmung beispielsweise infolge einer durchgemachten Infektion zurückzuführen sein.

Ein Umstand, der die Feststellung des wirksamen Allergens im Einzelfalle wesentlich erschwert, ist der, dass das allergisierende Moment nach KLINGE und RÖSSLE (zit. n. HEINILD³¹) keineswegs dasselbe zu sein braucht wie das auslösende, was bedeutet, dass die im Organismus gebildeten Antikörper nicht spezifischer sind, als dass sie mit einem anderen, möglicherweise nahe verwandten, Allergen reagieren und so die Krankheitserscheinungen auslösen können. Man muss wohl annehmen,

dass ein derartiger Mechanismus den zwar wenigen, aber doch typischen Fällen von Schönlein-Henochscher Purpura zugrunde liegt, die nach Erstimpfung beobachtet worden sind.

Ein Fall von Schönlein-Henochscher Purpura im Anschluss an Diphtherie-Schutzimpfung ist, soweit mir bekannt, bisher nicht beschrieben. Dass bei unserem oben wiedergegebenen Fall, bei dem die Erkrankung 2 Tage nach der Impfung auftrat, das Diphtherieanatoxin das auslösende Allergen gewesen sein muss, ist wohl ausser allem Zweifel. Dieser Impfstoff besteht ja aus einem durch Formalin teilweise entgifteten Diphtherietoxin, mithin aus einem Eiweisskörper, der an sich schon geeignet ist, als Allergen zu wirken, aber ausserdem noch aus anderem, von den Diphtheriebazillen synthetisierten Eiweiss sowie schliesslich zu einem Teil aus Nährbodeneiweiss von vorwiegend Peptoncharakter.* In der Hoffnung, bei unserer Patientin eine weiterbestehende Empfindlichkeit gegen dieses Anatoxin demonstrieren zu können, wurde mit diesem eine Kutanprobe (sog. Läppchenprobe) vorgenommen, aber mit negativem Resultat. Auch die intrakutane Injektion verdünnten Anatoxins in einer 0,001 ml entsprechenden Dosis rief keine *örtliche* Reaktion hervor, jedenfalls keine stärkere als bei Kontrollfällen. Dagegen erfolgte eine prompte Reaktion seitens des *Darms* in Form einer okkulten Blutung (Benzidinprobe + + +), wie sie zu dieser Zeit seit 2 Wochen nicht vorgekommen war, welche 4 Tage anhielt. Eine sichere allgemeine Hautreaktion resultierte nicht, da sich der nächste, auf die Fussrücken begrenzte Purpuraschub erst nach einem Intervall von 3 Tagen zeigte. Auf jeden Fall spricht wohl das erzielte Resultat für das tatsächliche Vorliegen einer Allergie gegen das angewendete Diphtherieanatoxin bei dem untersuchten Kinde.

Versuche einer passiven homologen Übertragung der Allergie nach PRAUSNITZ-KÜSTNER sowie DE BECHE durch intrakutane Injektion von Patientenserum bei zwei kürzlich gegen Diphthe-

* Laut Bescheid des Staatlichen Bakteriologischen Laboratoriums enthält gereinigtes Diphtherieanatoxin pro ml 0,15 mg Anatoxin, 0,15—0,30 mg anderes, von den Diphtheriebazillen synthetisiertes Eiweiss sowie etwa 1,25 mg Nährbodeneiweiss von vorwiegend Peptoncharakter.

rie geimpften Individuen fielen negativ aus. Es wäre naturgemäss interessant gewesen, das Phänomen der inversen Anaphylaxie nach VOSS und LI²⁵ durch intravenöse Injektionen von Purpurarekonvaleszentenserum in grösseren Mengen an zuvor gegen Diphtherie geimpften Versuchspersonen zu untersuchen. Die Arbeit von LI war mir jedoch in jener Zeit nicht erreichbar — und übrigens erscheint es nicht gerade zusagend, ein 3jähriges Kind der hierzu erforderlichen Blutmenge von ca. 200 ml zu berauben.

Dass also die Krankheitssymptome bei unserem Fall durch eine allergische Reaktion ausgelöst worden sind, darf als erwiesen gelten. Aber wie ist es hier von Anfang an zu dem allergischen Zustand gekommen; auf welche Weise ist der Organismus sensibilisiert worden? Dass es sich nicht lediglich um eine einfache Reaktion zwischen dem eingespritzten Diphtherieanatoxin und hierdurch bedingten Antikörpern handeln kann, geht schon aus der Tatsache hervor, dass die Krankheit bereits 2 Tage nach der Impfung ausbrach, mithin lange bevor erfahrungsgemäss Antikörper in nennenswerter Menge gebildet werden konnten. Überdies wäre es in diesem Falle durchaus unerklärlich, weshalb die Komplikation nicht häufiger auftreten würde. Schutzimpfungen gegen Diphtherie sind in unserem Lande zu Hunderttausenden vorgenommen worden, ohne dass meines Wissens Purpura in weiteren Fällen beobachtet worden wäre. Man könnte vielleicht einwenden, dass dies zum Teil auf der verhältnismässigen Neuheit dieser Art von Krankheitsvorbeugung beruhen könnte, dass nämlich die Zeit zur Veröffentlichung der gesammelten Erfahrungen nicht lang genug sei — aber das ist sicher nicht die ganze Wahrheit.

Da das Kind früher nicht gegen Diphtherie geimpft worden war, und da bei ihm auch keine SCHICKSche Reaktion angestellt worden war, kann es folglich nicht auf diesem Wege sensibilisiert worden sein. Auch die Anamnese liefert weder für eine allergische Stigmatisierung noch für erbliche Belastung irgendwelche Anhaltspunkte, und zwar im Gegensatz zu dem SEIDLMAYERSchen Material (16 Fälle), wo eine erbliche Belastung auf der Grundlage von exsudativer Diathese oder »Arthritismus« in der Ahnen-

reihe oder bei Geschwistern hundertprozentig vorgelegen haben soll. Eine direkte Heredität für die Krankheit als solche wurde jedoch nicht nachgewiesen, und in diesem Zusammenhang kann erwähnt werden, dass die 4jährige Schwester der Patientin gleichzeitig ohne die geringsten Komplikationen gegen Diphtherie geimpft worden war.

Offenbar hat sich unsere Patientin zur Zeit der Impfung in einer besonders empfindlichen Phase befunden, sie ist sensibilisiert gewesen, wobei das Wesen des allergisierenden Agens in tiefstes Dunkel gehüllt ist. In neuerer Zeit hat man auf pathologischem Gebiet der Bedeutung unspezifischer, sog. allergisierender Infektionen als pathogenetische Momente bei der Entwicklung einer Reihe von klassischen Krankheitsbildern, wie z. B. Polyarthritis, Glomerulonephritis, Kolitis, in steigendem Masse Rechnung getragen. Wenn sich also im Anschluss an eine Streptokokkenangina eine Polyarthritis mit sterilem Exsudat entwickelt, dann wäre dies ein Beispiel der Fernwirkung in Form einer unspezifischen hyperergischen Entzündung (RÖSSLE, EPPINGER, zit. n. HEINILD³¹). Die Möglichkeit, dass das Kind zur Zeit der Impfung eine leichte derartige Infektion durchgemacht hat, die symptomlos verlief, lässt sich nicht von der Hand weisen, aber hierfür kann auf der anderen Seite auch kein sicherer Beweis erbracht werden. Irgendwelche ausschlaggebende Anzeichen einer Infektion wies die Patientin nicht auf, es bestand weder Fieber noch Leukozytose, und die festgestellte Linksverschiebung sowie Erhöhung der Senkungsreaktion *können* durch die allergische Reaktion als solche verursacht gewesen sein. Jedenfalls muss man irgendeine Art von stummer Allergisierung annehmen, durch welche Antikörper zustande gekommen sind, die dann die Fähigkeit hatten, mit dem zugeführten Allergen zu reagieren, was in dem Krankheitsausbruch resultierte.

Zusammenfassung.

Es wird ein Fall von typischer Schönlein-Henochscher Purpura bei einem 3jährigen Mädchen beschrieben, bei dem die Erkrankung 2 Tage nach der Diphtherie-Schutzimpfung ausgelöst

wurde. Neben Hautblutungen traten Ödeme an den Gliedern, Gelenksbeschwerden, Kolikschmerzen mit okkultur Darmblutung und Hämaturie auf. Die Hautblutungen erschienen in mehreren (8) Schüben im Laufe von 5 Monaten, worauf das Kind gesund wurde. Die Lappchenprobe mit Anatoxin fiel negativ aus, aber nach intrakutaner Injektion einer Verdünnung desselben, 0,001 ml Anatoxin entsprechend, erfolgte eine prompte Reaktion seitens des Darms in Form einer Blutung. Damit wird die Rolle des Diphtherieanatoxins als auslösendes Allergen bekräftigt. Der Fall stellt einen Beleg für die Anschauung dar, dass die Krankheit anaphylaktisch bedingt ist, und rechtfertigt die Bezeichnung anaphylaktische Purpura an Stelle der alten Benennung anaphylaktoide Purpura. Er bestätigt hierdurch die Erkenntnisse, zu denen LI auf anderem Wege (durch die inverse Anaphylaxie) gelangt war.

Der dargestellte Fall dürfte der erste von Schönlein-Henochscher Purpura sein, der nach Diphtherie-Schutzimpfung beobachtet — oder jedenfalls beschrieben — worden ist.

Schrifttum.

1. MORAWITZ, P.: zit. SCHOCH, M. A.: Neue Ergebnisse in Klinik und Pathologie der Hautblutungen. Schweiz. Med. Woch.schr. 21, 1940. S. 25—29, 49—53. — 2. CATEL, W.: Blutungsübel im Kindesalter. Fol. haematol. 63, 1939—40. S. 328—353. — 3. VAHLQUIST, B.: Om hämorrhagiska diatheser i nyföddhetsperioden. Sv. Läk.tidn. 39, 1942. S. 280—294. — 4. BEXELIUS, G.: Acta Med. Scand. 80, 1933. S. 281. — 5. GÖTHLIN, G.: Det infradiastoliska kapillärprovets tekniska utveckling. Nord. Med. 23, 1944. S. 1327—1336. — 6. HOET, J. P. en van VYVE, A.: Prothrombingehalte gedurende het beloop van purpura van Henoch-Schönlein en de behandeling met methyl-derivaten van naphthochinon. Nederl. Tijdschr. v. Geneesk. 84, 1940. S. 1777. — 7. SCHAAD, H.: Vitamin K in einem schweren Fall von Purpura rheumatica. Schweiz. Med. Woch.schr. 71, 1941. S. 1622. — 8. AUBERTIN, C.: Signe de lacet négatif chez des malades en pleine eruption purpurique. Bull. et Mém. de la Soc. méd. des Hôpitaux de Paris. 56, 1940. S. 375—376. — 9. JERSILD, T.: Therapeutic effect of vitamin P in Schönlein-Henoch purpura. Lancet. 234, 1938. S. 1445. — 10. SEIDLMAYER, H.: Die frühinfantile postinfektiöse Kokarden-Purpura. Zetschr. Kinderheilk. 61, 1939. S. 217—255. — 11. FINKELSTEIN: zit. SEIDLMAYER. — 12. GLANZMANN, E.: zit. SEIDLMAYER. — 13. GLANZMANN, E.: Zum Problem der Purpura fulminans. Schweiz. Med. Woch.schr. 18 (67), 1937. S. 829—830. — 14. BERG-

- GREEN, P.: Zur Kenntnis der Schönleinschen Purpura. *Dermat. Woch.schr.* 111, 1940. S. 1076—1078. — 15. HENOCHE, W.: *Klin. Woch.schr.* 11, 1874. S. 541. — 16. DUSCH und HOCHÉ: zit. WASSILIEFF. — 17. FRANK, E.: *Klin. Woch.schr.* 52, 1915. S. 454. zit. HAMPTON. — 18. GLANZMANN, E.: *Jahrb. Kinderheilk.* 83, 1916. S. 271. — 19. SEIDLMAYER, H.: Sippenforschungen bei Trägern von Schönlein-Henochscher Erkrankung. *Zeitschr. Kinderheilk.* 61, 1939. S. 488—502. — 20. SCHWARTZMANN, J.: Henoch's purpura with intussusception. *Arch. Pediat.* 57, 1940. S. 389—394. — 21. ALTHAUSEN, T. L., DEAMER, W. C. and KERR, W. J.: False "acute abdomen". Henoch's purpura and abdominal allergy. *Ann. Surg.* 106, 1937. S. 242—251. — 22. BARNES, C. and DUNCAN, G.: Anaphylactoid purpura simulating acute regional ileitis. *Brit. J. Surg.* 29, 1941—42. S. 253—255. — 23. HAMPTON, S. F.: Henoch's purpura based on food allergy. *J. Allergy* 12, 1941. S. 579—591. — 24. KERN, R. A.: Discussion. *J. Allergy* 12, 1941. S. 591. — 25. LI, Min-sen: Zur Frage der anaphylaktischen Genese gewisser Purpuraerkrankungen. *Monatschr. Kinderheilk.* 88, 1941. S. 63—68. — 26. MARITSCHKE, M. und MARKOWICZ, H.: zit. HEINILD. — 27. LOEWY, F. E.: *Lancet* 226, 1934. S. 845. — 28. FALCONER, E. H. and SCHUMACHER, I. C.: *Arch. Int. Med.* 65, 1940. S. 122. zit. HEINILD. — 29. MEULENGRACHT, E.: Purpura haemorrhagica efter Brug af Sedormid. *Ugeskr. f. Læger* 103, 1941. S. 291—295. — 30. THIELE, W.: Akute thrombopenische Purpura nach Sedormid- und Saridongebrauch. *Münch. Med. Woch.schr.* 89, 1942. S. 934. — 31. HEINILD, S.: Undersøgelser over de kvantitative Variationer i Blodpladetallet under Anaemi, Infektion og Thrombopeni. København 1942. 395 S. — 32. WALDENSTRÖM, J.: Purpura hyperglobulinaemica. *Nord. Med.* 23, 1944. S. 1562—1565. — 33. WASSILIEFF, P.: Om patogenesen af Schönlein-Henoch's Purpura. *Nord. Med. Tidsskr.* 14, 1937. S. 1322—1325. — 34. RAMB, H.: *Zentralbl. f. Chir.* 68, 1941. S. 1973—1975. — 35. RYANG, W. T.: An autopsy observation of a case with Henoch's purpura. *J. Chosen med. Ass.* 27, 1937. S. 33. — 36. HAAG, F. E.: Neuere Ergebnisse der Allergieforschung. *Münch. Med. Woch.schr.* 89, 1942: 2. S. 752—758. — 37. DUKE, W. W.: *Arch. Int. Med.* 28, 1921. S. 151. zit. HAMPTON. — 38. ALEXANDER, H. L. and EYERMAN, C. H.: zit. HAMPTON. — 39. SQUIER, T. L. and MADISON, F. W.: *J. Allergy* 9, 1937. S. 143. — 40. LANDSBERGER, M.: *Zeitschr. Kinderheilk.* 39, 1925. S. 569. — 41. HEATON, T. G.: Purpura associated with vaccination against smallpox. *Canad. Med. Ass. J.* 43, 1940. S. 593—594. — 42. HEINILD, S.: Purpura infectiosa allergica. *Nord. Med.* 20, 1943. S. 2302—2305. — 43. REGAMEY, ELISABETH: Crise aigue de purpura thrombopénique consécutive à une généralisation vaccinale tardive. *Schweiz. Med. Woch.schr.* 21: 2, 1940. S. 697—699. — 44. WEINGÄRTNER, L.: Purpura Schönlein-Henoch als Folgeerscheinung einer Erstvakzination. *Kinderärztl. Praxis.* 12, 1941. S. 39—41.



Abb. 1.



Abb. 2.

F

w

y

d

s

y

n

C

f

t

a

a

I

c

C

b

v

n

l

n

n

l

i

A Sex-linked Type of Gargoylism.

By

ARNE NJÅ.

In 1917 HUNTER (6) described the first case of a condition with multiple malformations, especially of the skeleton. Two years later the next publication concerning two cases of this disease came from GERTRUD HURLER (7). During the first subsequent years reports of similar cases were sporadic, but in recent years reports of the so-called *Hurler's syndrome* have become more numerous, especially from America, England, Holland and Germany. No case of this disease has previously been published from Norway.

The many names which the various authors have designated the disease have caused some confusion. The Germans call it *dysostosis multiplex*. In America the designation *Lipochoondrodystrophy* has been used in recent years. The name which has probably become best known, is *gargoylism*, a name which is due to the similarity to the grotesque figures on Notre Dame Cathedral in Paris.

The condition is characterized by malformations of the head, body and extremities, especially of the skeleton, malformations which give the patient a grotesque appearance. The children are normal at birth but usually have a heigh birth weight. Dwarf-like growth gradually develops. By the age of one year the children usually show the characteristic appearance. The head is remarkably large, often of a peculiar shape. The sutures are prominent. The nose is broad and flat, the lips thick, and the large, fissured tongue often hangs out of the mouth. The neck is very short. The most prominent aspects of the trunk are the

large abdomen and the lumbar kyphosis which is almost constantly present. The extremities are short, coarse and thick. There are often irregularities in the joints, so that the function is limited. This is usually most pronounced in the shoulder joints so that the arms cannot be raised above the horizontal, and in the fingers, where the outer phalanges remain in flexure contraction with the exception of the thumb. Corresponding to the described alterations a number of typical skeletal alterations are revealed by roentgen examination. The liver and the spleen are almost always enlarged. There are often umbilical and inguinal hernia. In most of the patients the corneae are uniformly cloudy. Many of them have a marked hypertrichosis.

In recent years it has been demonstrated that one of the essential features of the disease is a pathologic lipid metabolism (KRESSLER and AEGERTER, 10). One of the steps in this process may be some special granula which have been demonstrated in the white blood corpuscles of patients suffering from gargoylism (REILLY, 17). An increased cholesterolin content in the blood may also be observed in this connection.

The patients are very susceptible to catarrhal infections of the respiratory organs. Purulent rhinitis and rhinopharyngitis especially are typical. As a result of this the respiration is often loud and snoring. Bronchitis and bronchopneumonia are also common. Their hearing is often poor, their intelligence usually low. However some cases of patients with normal intelligence have been described (11, 14).

Nothing is known as to the cause of the disease. Many of the patients described are isolated cases. However there seems to be a tendency to familial incidence (4, 11, 12, 15, 18). The parents have occasionally been related. These observations have led to the assumption that the condition is hereditary, due to recessive genetic factor.

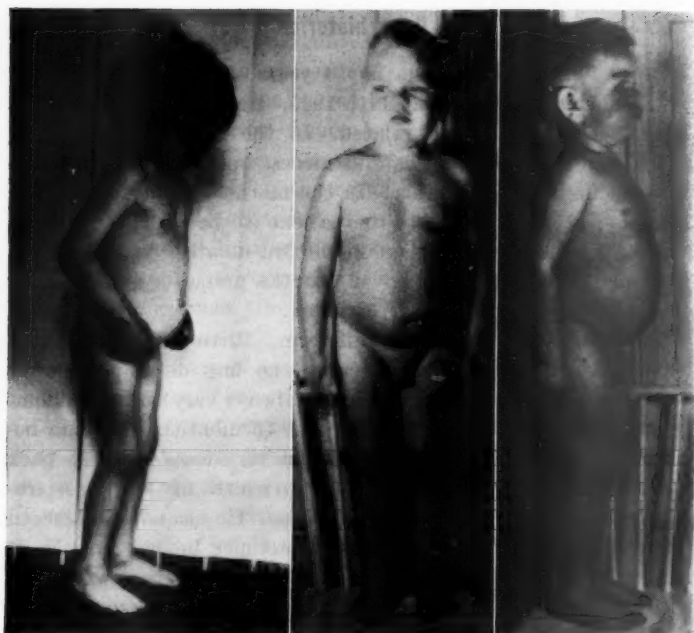
There are still so few reports of this peculiar condition that every new case may contribute to our knowledge of it. At the Pediatric Department of the Rikshospitalet we recently had the opportunity of examining some patients suffering from gargoylism.

Case histories.

Case 1 (III, 2). B. G., a boy 4 years old, who was admitted to the Pediatric Dept. May 11th 1945. He is an only child. The parents are healthy, not related. In the fathers family there are several imbecil nephews and nieces, but none of them presents an unusual appearance. In the mothers family there have been several cases similar to the patient (to be described below). The mother had a miscarriage in the 3rd month 6 years ago. In 1940 she gave birth to a boy 2 months prematurely. He died of cerebral hemorrhage after 11 hours.

The patient was born at full term. Birth weight 4 120 gr, length 53 cm. From early infancy the boy developed slowly both physically and mentally. He was always very quiet, could not sit until he was a year old, walked at 16 months. Teething began at 4 months. The mother noticed very early that his back was remarkably bent. A short time after birth his heavy respiration and hoarse voice attracted attention. He has not yet learned to talk. His humour is variable, sometimes he has attacks of rage. His sight is good, but his hearing poor. His appetite has been tremendous. It is striking that he has had pneumonia 5 times. During the last year he has been unable to straighten his fingers.

Condition on admission May 11th 1945 (fig. 1). The boy makes a peculiar impression. He is of normal height, but very fat. (Height 103 cm, normal 104 cm, weight 24.6 kg, normal 17.5.) The head is large (circumference 54 cm, average for his age 50 cm). The forehead is somewhat bulging, especially in the middle part. The nose is broad and flat, the lips coarse and thick. The neck is very short. Sitting up he shows a slight thoraco-lumbar kyphosis. The 4 ulnar fingers cannot be straightened. These fingers are also slightly bent in a radial direction. He is slightly knock-kneed. Otherwise there are no deformities of the extremities and no limitation of the movements of the joints. He walks with good balance. Psychically he is far below normal, cannot talk. His breathing is loud with hoarse, snoring wheezes, frequency 20 per minute. Pulse 104, regular. The



Case 6.

Fig. 1.

Case 1.

mucous membrane of the fauces is hyperemic, and a moderate amount of thick mucous is observed on the posterior wall of the pharynx. His teeth are good but are rather far apart. The pupils are round, equal and react to light. The cornea is clear on both sides. Thorax: No malformations. Lungs: Stentorous respiration, otherwise nothing pathological. Heart: A slight systolic murmur. The abdomen is very large. There is a scare after an operation for umbilical hernia. The hernia has broken out again. The liver and the spleen are moderately enlarged. The external genitals are somewhat underdeveloped, and both testicles are retented. He does not seem to hear normal.

Blood analysis showed: Hgb. 85 %. Red blood corp. 5 mil-

lions, white blood corp. 7 200. Blood sedimentation rate 12 mm. By differential count normal conditions were found, and a sternal puncture revealed normal distribution of the cells. No pathologic granulation of the cells could be demonstrated neither in the blood nor in the bone marrow. Calcium: 11.60 mg%. Phosphorus: 4.29 mg%. Cholesterin: 180 mg%. Urine: Normal. Pirquet's reaction negative. Wassermann's reaction negative.

The roentgen examination was made by J. TORGERSEN who gave the following description: »In the thoraco-lumbar column a slight kyphosis and a scoliosis can be demonstrated. The vertebral corpora, especially in the lower part of the thoracic column, are biconvex. The peculiar shape of the lower ribs is striking. The broad, flat rib attached to the spine by a narrow cervix gives an impression of a palm-leaf. The picture is characteristic of gargoylism. Hands: The phalanges are abnormally broad, especially basally. The cranium is large, of normal shape, normal sutures. The bone seems somewhat transparent. The sella turcica is flat and elongated. The dorsum sellae seems to lack calcium.»

Case 2 (II, 2). S. H., brother of Case 1's mother, was admitted to the Pediatric ward in September 1912, 9 $\frac{1}{2}$ years old, and remained there, with a short interval, until he died in September 1914. This case is of particular interest because the record presents a convincing description of the syndrom several years before the first report was published, and because a post mortem examination was made.

The child was born at full term and had a normal delivery. He was said to be of normal size and his face was pretty. Teething began at 9 months. About the same time he had bilateral otitis media. From that time the mother noticed that the boy's head was large and that he did not seem normal for his age. About the age of 1 year he had occasional short spells of unconsciousness without spasms. He began to say single words when a year old. But at 3—4 years of age he stopped talking completely, and the last few years before admission he had been quite dull. He began to walk when he was 2. At 3—4 years of age he had bronchopneumonia. When he was 4—5 he spent several months

in bed with fever and vomiting. His mother believes that he has been deaf for the last few years. He has not been interested in anything except food. His extremities have been thick, cold and blue since infancy. The size of his head did not increase very much after the age of 2 when the circumference was 54 cm. He had always been incontinent.

State on admission Sept. 29th 1912: The child is an idiot. The head is large with abundant, coarse hair growing far down over his forehead and temples. The back also is hairy. The frontal bone forms a vertical comb in the median line. His face looks old and repulsive, with broad, flat nose, pronounced epicanthus and confluent eyebrows. The lips are thick and cyanotic. The tongue is thick and hangs out of the mouth. The neck is very short. No abnormalities of the thyroid gland can be demonstrated. The extremities are stubby, cold and cyanotic. The motility is considerably limited in the foot, the knee and the elbow. The distal finger joints are almost completely stiff, slightly bent. The 4 ulnar fingers are curved with concavity toward the radial side. Pulse 96, regular. Respiration 24. Pupils equal, react to light. Lungs: Diffusely spread ronchi. Heart: Nothing special. Abdomen: The liver is considerably enlarged with the lower edge palpable at the umbilical transversal. There is a more than nut-sized umbilical hernia and on the right side a large inguinal hernia. He walks without assistance.

During his long stay at the hospital he had measles, whooping cough and scarlatina, and frequently suffered from infections of the respiratory tract. He died during an attack of cyanosis and dyspnoea in Sept. 1914. The case was interpreted as myxidioti, and he was treated with thyroid gland the whole time without effect. A roentgen picture of the elbow showed abnormal epiphyses. The bone nuclei of the hand were normal developed. There are no remarks in the record as to the column or the cornea. His height is not given, but his weight was only 22.6 kg (post mortem) as compared to the normal of 36 kg for his age. As his body stubby it may be concluded that he was very short, which is also indicated by photographs (fig. 2).



Fig. 2. Case 2, 11 $\frac{1}{2}$ years old.

The *post mortem examination* revealed the following: The circumference of the *head* and the chest are about the same, 58—59 cm. The sagittal suture and the frontal and the occipital tubera are very protruding. The cranium is thick, heavy, the skull weighs 680 gr. The sawed surface shows very fine pores, and there are some sclerotic regions. The basis of the cranium is abnormal: The bone is very thick, and the orbital roofs have protruding hemispheres of compact bone more than 1 cm thick. The os ethmoideum is depressed. The sella turcica is wide and flat. No diminution of any of the holes for the facial nerves. The *brain* is large with a marked hydrocephalus internus. The thin cerebral membranes are thickened and milky.

The *chest* is unelastic, the ribs thick with an abnormal shape, but they show no signs to rickets. The breast bone is very hard and compact. *Extremities* short, hands and feet large, fingers and toes short and broad. The right tibia is removed. It is atrophic, abnormally bent in the proximal part. The corticalis is thin, and the spongy tissue is more porous than normal.

The *thymus* extends from the jugulum to the diaphragm. Weight 41 gr. The *heart* weighs 140 gr. The left ventricle is somewhat hypertrophic and the right ventricle is dilated. The myocardium seems normal. The aortic valve is thickened, but without excrescences, and there is no retraction. The mitral valves are thick with knotty borders. The cordae tendineae are short and thick. In the aorta scattered plaques of fatty degeneration are observed. The walls of the bronchi are thick, and their mucous membrane is hyperemic and coated with mucopus. The lymphatic tissue is hypertrophic in the respiratory tract, and also the mucous membrane of the stomach and the intestines shows numerous, large lymph follicles. The thyroid gland weighs 31 gr. The *spleen* is much enlarged, weight 215 gr — the structure is irregular with hypertrophic follicles. The *liver* is tremendous, weight 1 280 gr. On section the structure appears to be normal. The pancreas is a bit large, weight 80 gr. Kidneys and adrenals seem normal.

Microscopic examination: The *bone substance* in the cranium is very compact with relatively large marrow cavities which are partly blocked by bone deposits, in many places to such an extent that the marrow cavities are practically filled. The structure of the compact bone substance is irregular. The *hypophysis* is of normal size. In the glial region and the infundibulum the structure is normal. At the transition to the epithelial part there are some cystous cavities lined with a cylinder epithelium. The epithelial region is of normal structure. The substance of the *thymus* consists of extremely numerous small cells, most of them similar to lymphocytes. In large areas the Hassal's bodies are lacking. The *pancreas* parenchym is diffusely degenerated. It is irregular in structure without the usual distinct lobuli. The islands of Langerhans are not distinct. There are no vi-

sible ducts. Sections from the skin, adrenals and thyroid gland were normal. There is no description of the liver.

Case 3 (II, 9). O. H., younger brother of Case 2, was admitted to the Pediatric ward in May, 1922, 4 years old. He was born at full time. Birth weight 3 250 gr. His appearance was normal. From the time he was 4 months he grew constantly fatter. At this time he was treated for «rickets». From the age of 7 months he constantly suffered from infections of the respiratory tract. When he was 2 years old the diagnosis myxoedema was made. He took thyroid tablets for 1 1/2 year without result. He is incontinent.

Condition May 4th 1922. The patient is fat. He is able to walk, but cannot talk. The head is large with a protruding forehead, especially in the median line. The bridge of the nose is sunken, and the nose is short and broad. The lips are thick and the large tongue hangs out of the mouth. His face is coarse with the typical expression of an idiot. He has almost no neck as if the head were attached to his shoulders. His hair is red, short and dry, growing far down in the forehead and the temple region. There is also a great deal of hair on the upper part of his back. The extremities are short, especially are the fingers and the toes short and broad. The feet are cold and cyanotic. The pupils are equal, react to light. The breathing is laboured and audible. The tonsils are enlarged, converging. Muco-pus in the pharynx. The teeth are carious, some of them extracted. The thyroid gland is not enlarged. Lungs: Dispersed ronchi. Heart: Normal. Abdomen large. The edge of the liver is palpated 2 fingerbreaths below the costal arch. Spleen not palpable. He stayed at the ward for little more than a week. There are no records of any further examinations or comments of the case. The diagnosis was myxidioti.

In July, 1925 he was admitted again, 7 years old. Since his last hospitalization he had had pneumonia and frequent attacks of dyspnoea and restlessness with vomiting. He had gradually grown duller. He was thought to be practically moribund on admission. The following symptoms not recorded the first time are: There is a prominent vertical bone protrusion corresponding

to the sagittal suture. The outer phalanges of the fingers are bent like claws. The liver is extremely enlarged. The spleen is very hard and extends 4 cm below the costal arch. There is a large inguinal hernia on either side. Wassermann's reaction negative. Sahli (uncorrected): 70. Red blood corp. 5.4 mill. White blood corp. 7 000. Roentgen examination of the hand showed 6 bone nuclei. The epiphyses were thick and irregular, but there were no signs to rickets. Nothing is recorded as to height, column, motility of the joints (except the fingers), cornea. There is no photograph of him. His sisters say that he was small, like his brother. He was discharged with the diagnosis myx-idioti, and died in 1928 at a home for feeble-minded.

Case 4 (III, 5). P. J., maternal cousin of case 1. We are told that he resembled exactly the 3 described above. He was an idiot, spoke only a few words, was very short and had a large head. He grew gradually duller and died in 1942 at the age of 11. Amateur photographs show that his appearance is quite identical with the two patients first described.

Case 5 (III, 4). J. P. B., a maternal cousin of patients Nos. 1 and 4. This patient was examined by the author in September 1945 (fig. 3). He was born April 26th 1944. Birth weight 3 595 gr. At birth he appeared perfectly normal. His head gradually grew large, and his back bent. Teething began at 6 months. He walked at 14 months. The mother believes that he is mentally backward. He has not begun to talk. His breathing has always been audible. The patient was called in for examination because of the other cases in the family, and the parents did not wish to have him hospitalized.

He is a fat, coarsely built boy of 1 $\frac{1}{2}$, of average height for his age (82 cm). Weight: 13 600 gr (normal for his height: 11 900 gr). The head is large, circumference 53 cm. There is a keel-like comb of bone in the midline of the forehead extending backward to the fontanell, which is just closed. The features are coarse with a broad, flat nose, and thick lips. His tongue is not particularly large. Cornea clear on either side. No hypertrichosis. The neck is very short, the body stubby. There is a gibbus in the upper part of the lumbar column. Rasping respiration is



Fig. 3. Case 5.

heard bilaterally, the heart seems normal. The abdomen is covered by a thick layer of subcutaneous fat, the liver and the spleen are much enlarged. The motility of the shoulder joints is considerably limited. Otherwise there is no demonstrable limitation of the mobility in any of the joints. The hands and fingers are short, but otherwise of normal shape. The fingers can be moved normal.



Fig. 4. Case 5. Kyphosis due to the deformed 2nd lumbar vertebra.

Roentgen examination (made by Dr. J. TORGERSEN): «Corresponding to the corpus of L 2 there is a kyphosis, due to a peculiar shape of this corpus (fig. 4). There is also a slight S-shaped scoliosis of the entire column. The picture is typical of gargoylism. The ribs are normal.» Further examinations were not allowed by the parents.

Case 6. A. J. L. a $4\frac{1}{4}$ years old girl, admitted to the Pediatric ward May 28th 1945 for observation of a «dysendocrine affection». No similar cases are known in the family. The parents are not related. The mother has 4 siblings with a total of 2 children, and the father has 7 siblings with 6 children, all healthy. The patient is an only child. She was born at full term, the delivery was normal. Birth weight 4 500 gr. It was early obvious that the child was not developing normal. She began to walk

at 1 $\frac{1}{2}$, spoke fairly well at the age of 3. The parents finally consulted a doctor when they noticed that the child's fingers had become abnormally bent.

In the ward the child was found to be of normal height (106 cm). Weight 19.6 kg (normal for her height 17.5 kg). Her appearance is peculiar (fig. 1). The head is large (circumference 54 cm), the face coarse with a broad, short nose and thick lips. The eyes are set far apart. The ears are large, deformed and placed low on the head. The hair is abundant, and she has a good deal of dark hair on her back and shoulders. The body is stubby with protruding abdomen, the neck is very short. Her limbs are also short, the hands large with short, broad fingers. The distal phalanges of the 4 ulnar fingers cannot be straightened, and they deviate in radial direction. The skin of the hands is shiny and slightly atrophic. The arms can only be lifted slightly over the horizontal. The mobility of the elbow joints is also limited. The corneae are uniformly cloudy. The respiration is normal. Tonsils moderately hypertrophic. The tongue is large, but does not hang out of the mouth. No abnormal distance between the teeth. Thorax: Somewhat broad in the upper part, and there is a slight depression of the lower part of the sternum. Heart and lungs: Normal. Abdomen: A nut-sized umbilical hernia. Liver and spleen large. The hearing is reduced, and otoscopy reveals shrunken ear drums. Special examination of the eyes: Over the entire cornea on either side there are small gray spots and fine gray lines. They appear to be situated in the anterior half of the cornea. There are no vessels, no iritis. The retina is not clearly visible. Conclusion: The shadows are probably due to degeneration.

Blood analysis: Hgb. 90 %. Red blood corp. 4.01 mill. White blood corp. 7 300. The blood and the bone marrow showed normal distribution of the cells, and no pathological granula could be demonstrated. Blood sedimentation rate 6 mm. Calcium: 11.83 mg%. Phosphorus: 5.54 mg%. Cholesterol: 232.5 mg%. Urine: Normal. Wassermann's reaction negative.

Roentgen examination: The cranium is large with a protruding forehead. The sella turcica is long and shallow. The proxi-

mal part of the radius is broader than normal. The upper part of the humerus is also remarkably coarse. The atypic bone configuration is due to an abnormal size and shape of an independent epiphysis of the tuberculum majus. The epiphysis of the caput appears to be rather flat. The distal radius and ulna epiphyses are crooked and deformed. The bone nuclei of the hand are normally developed. The column shows a slight biconvexity of the vertebrae. The lower ribs have a tendency toward the characteristic palm-leaf shape.

Discussion.

Diagnosis. All the described patients exhibit so many common symptoms that it seems justified to classify them in the same group. Their deformities check up feature for feature with those described as typical for gargoylism. There are in fact no other differential diagnostic possibilities. These patients are often misinterpreted as suffering from rickets or myxidioti. Both these conditions can be definitely excluded. We do not find the symptoms typical for these affections either on clinical or roentgen examinations. Two of the patients were treated under the diagnosis myxidioti at the Pediatric ward because of the superficial similarity and because of the lack of any other adequate diagnosis. The first patient died several years before the first description of gargoylism was published.

Occasionally these cases are confused with MORQUIO's disease. This malformation, which have several features common with gargoylism, can readily be distinguished from the latter by the typical thorax deformity and by the fact that these patients have a normal intelligence. LAHDENSUU (11), however, is of the opinion that transition forms exist, based on the observation of 4 cases in one family. These patients exhibited the typical signs of gargoylism, but their intelligence was normal.

In a condition which has so many symptoms as this one it is reasonable to expect some variation in the individual cases. Cloudy corneae have been considered to be a constant symptom. This symptom was not present in the cases belonging to the

family first described. The question whether the absence of this symptom makes it necessary to interpret such patients as a distinct type, has been discussed previously by CORNELIA DE LANGE and co-workers (12, 13). Several cases with normal corneae have been described, and most of the authors tend to regard them as true cases of gargoylism. This question will be discussed in more detail under the discussion of heredity.

The characteristic kyphosis may be absent as in our Case 6, who is otherwise typical. Gargoylism has been characterized as a disproportionate dwarf development. This is not quite in agreement with the facts now available. SHELDON (19) describes a case in a 3 years old boy who was taller than normal for his age, JEWESBURY and SPENCE (9) have a case of a boy of $5\frac{1}{2}$ of normal height. One of CORNELIA DE LANGE's patients was also of normal size. Of our patients, 3 are of normal height, a girl of $4\frac{1}{2}$ and 2 boys aged 4 and $1\frac{1}{2}$, while the others exhibit dwarf-like growth. At birth the children are of normal size or larger. The delayed growth has its onset at various age (1—5 years of age) in these patients.

The post mortem observations. There are to date only a few reports of post mortem examinations of gargoylism (2, 3, 10, 13, 20). BINSWANGER and ULLRICH (3) report the post mortem findings in one of HURLER's first patients. The observations in our patient, from 1914, agree in many features with HURLER's but differ also in some important points. Common to both is an enlarged brain with a considerable hydrocephalus. A compact, sclerotic bone substance is also common to both. In HURLER's patient the skull was thin with deep impressions, so that it was almost membrane-like in some regions. In our patient the heavy, thick, sclerotic skull with a depth up to 1.5 cm was striking. A further peculiar feature of our patient was the abnormality of the base of the cranium with the large, thick orbital roofs reaching up into the cavity of the skull. Another feature which should be emphasized, is the wide sella turcica, a finding which confirms the observations regularly made in roentgen examinations of these patients.

KRESSLER and AEGERTER's (10) description of their observa-

tions by microscopical examination is of particular interest for the etiology and pathogenesis. They have demonstrated that there is an infiltration of an unknown substance in and between the parenchyme cells and the fibrous cells in almost all of the organs. No detailed chemical analysis of this substance has been possible but it is interpreted as a lipoid. The affection thus seems closely related to the lipoidoses: amaurotic idiocy, Gaucher's disease, Niemann-Pick's disease, Hand-Schüller-Christian's disease.

We studied the description of the microscopical findings from our patient from 1914 with great interest. Unfortunately the report gives no indication that similar infiltration of the organs was observed there. But this description must be considered with certain reservations, as things to which attention is not particularly directed may readily be overlooked. However there are other investigators who have looked for lipoids without finding them. CORNELIA DE LANGE and co-workers (13) found a perfectly normal brain in a patient with gargoylism. In the liver they found glycogen, not lipoids. These findings were made in a patient with normal corneae, and this case is emphasized particularly by the authors in the discussion on the justification of setting up subdivisions of gargoylism.

In addition of the above-mentioned features the massive lymphocyte infiltration of several of the organs should be pointed out, especially the thymus and the respiratory and digestive tracts. This was striking both macroscopically and microscopically.

The Heredity of Gargoylism.

As mentioned above, it has been assumed that the condition is due to an autosomal, recessive hereditary factor. How does this agree with the findings in our family? Let us examine the family more closely as presented in fig. 5. The patients affected with gargoylism are presented in black, assumed bearers are designated \odot . Of the original couple we know that they were healthy and not related. The father had grown up in an orphan asylum. His origin is unknown. Two of his sisters are said to have been healthy. Otherwise we have no information of his

family. In the mother's family similar cases had not been seen previously. She had many healthy sibs who had only healthy children. They had 11 children:

II, 1. She is the mother of our case 1, B. G. She had previously had a son who died of cerebral hemorrhage 11 hours after birth.

II, 2. S. H., our case 2, who died at the age of 12 in 1914.

II, 3. Mother of our case 5, J. P. B. In addition to this son she has an older healthy daughter.

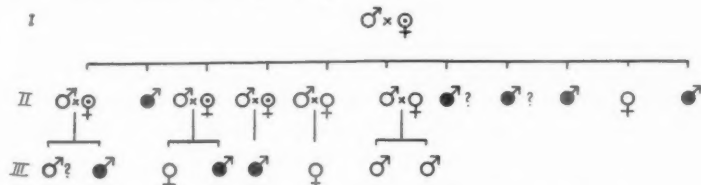


Fig. 5. Patients affected with gargoylism are presented in black, assumed bearers are designated ♀.

II, 4. Mother of our case 4, P. J., who died at the age of 11 in 1942. She has no other children.

II, 5. A woman who has a healthy daughter, no sons.

II, 6. A son who is healthy and has 2 healthy sons.

II, 7 and 8. Two boys who both died at the age of 6 months, cause unknown. The surviving siblings claim that these two resembled the two who had been at the pediatric ward. They died so young that symptoms of gargoylism could not have been very pronounced. Whether these two suffered from the affection cannot be determined.

II, 9. Our case 3, O. H. died in 1928, aged 10.

II, 10. A daughter 24 years old, single, healthy.

II, 11. A son born 1923, died 1926. He had the same appearance and malformations as his other sick brothers. He also suffered from laboured, audible breathing.

In summing up we see that 3, possibly 5 of the boys are affected by the hereditary disease, while 1, possibly 3, were unaffected. Of 5 daughters all are normal, but 3 of them have sons suffering from gargoylism, and are assumed to be bearers of the

affection. The other 2 daughters, one of which has a daughter and the other one no children, may be entirely free of the factor, but the possibility remains that they too are bearers of the gene.

All these facts definitely indicate that the disease is due to a sex-linked recessive factor in this family. This explains why all of the individuals affected are boys, who have inherited the affection from a healthy mother, and why it appears so frequently although there is no consanguinity. The parents were unrelated in all of the cases described. On the assumption that a female carrier of the gene marries a healthy man, it is expected when there is a sex-linked recessive heredity that one half of the sons will be affected and the other half healthy, free from the particular factor involved. Of the daughters half of them should be healthy and without the factor, half of them healthy carriers of the factor. In the family described the affection occurs more frequently, but the figures are too small to allow any conclusions as to the distribution. However the figures are not in any disagreement with the above hypothesis. One point which support the theory is that the only son in the family who had reached maturity has 2 healthy sons, while 3 of the married daughters each has an affected son.

This type of heredity in gargoylism has not been described previously. It is therefore logical to take up the question as to whether various types of gargoylism can be distinguished. Clinically our patients have all the main characteristics and details of classic gargoylism except one: Their corneae are normal, and cloudy corneae were originally considered as a symptom indispensable for the diagnosis. Some cases have been described where this symptom is lacking, but these have nevertheless been accepted by later authors. Such cases are reported by CORNELIA DE LANGE and WOLTRING (12), by COCKAYNE (4), by LURIE and LEVY (15) and by ROSS, HAWKE and BROWN (18). All of these patients are boys and it is particularly interesting that all of the publications mentioned above concerne two brothers (not twins). Thus it appears that in these cases also a recessive, sex-linked factor may be involved. Accordingly it seems justified to distinguish a special type of gargoylism, a *sex-linked, recessive form where*

the corneae are clear, but which otherwise satisfies all the requirements necessary for diagnosis. It also seems possible, according to our present knowledge, that the lipoid deposits are lacking in this particular type.

It is not an unknown phenomenon in medicine that a disease, which appears to be identical with another is of an entirely different origin. Morbus LAWRENCE-MOON-BIEDL, which is hereditary, can, with the exception of the polydactyly, seem identical with dystrophia adiposo-genitalis (FRÖHLICH) which is of endocrine origin. In Morbus MORQUIO the heredity is sex-linked recessive, and this condition is therefore found almost exclusively in boys. However TORBEN ANDERSEN (1) has described a case in a girl. There were no other cases in the family, but the parents were related. At the pediatric ward of the Rikshospital we have recently had the opportunity to observe a typical case of MORQUIO's disease in a girl (to be published later). This was also the only known case in the family and the parents were not related. These indications seem to indicate that morbus MORQUIO can also occur with apparently identical cases due to a different way of hereditary.

In a material of gargoylism (10) it appears to be more frequent in boys. This may be explained by the fact that the equal distribution which the recessive, non-sex-linked type of hereditary gives, dominates the material, while the excess of boys appears because some of the cases belong to the special sex-linked type where only boys are affected.

That the same phenotype may occur on the basis of various kinds of heredity has also been observed in experimental genetics.

In our material the affection should accordingly come from the above described mother of the family. The factor must either have been present in her family previously, although the information we have of her numerous healthy relatives indicates the contrary, or it is possible that the factor originated in her as a mutation.

Summary.

The author gives a resume of the symptomatology of gargoylism. 6 cases are reported. 5 of them belong to the same family. All of these are boys and none of them had cloudy corneae. A pedigree shows that the affection is inherited from a healthy mother and is probably sex-linked. The author therefore believes that it is justified to set up a special sex-linked type of gargoylism where the corneae are normal.

References.

1. ANDERSEN, T.: Dansk Pædiat. Selskabs Forh. Ugeskrift for Læger 1937, p. 169. — 2. ASHBY, W. R., STEWART, R. M. and WATKIN, J.: Brain LX, 2, 1937. Cit. Waardenburg. — 3. BINSWANGER, E. and ULLRICH, O.: Zeitschr. f. Kinderheilk. LIV 1933, p. 699. — 4. COCKAYNE, E. A.: Proc. Roy. Soc. Med. 30, 1936, p. 104. — 5. HELMHOLTZ, H. F. and HARRINGTON, E. R.: Am. J. Dis. Child. Vol. 41, 1931, p. 793. — 6. HUNTER, C.: Proc. Roy. Soc. Med. 10, 1917, p. 104. — 7. HURLER, G.: Zeitschr. f. Kinderheilk. XXIV 1919, p. 220. — 8. JACOBI, M. L. and WAARDENBURG, P. J.: Maandschr. v. Kindergeneesk. nr 5, 1940, p. 175. — 9. JEWESBURY, R. C. and SPENCE, J. C.: Proc. Roy. Soc. Med. 14, 1921, p. 27. — 10. KRESSLER, R. J. and AEGERTER, E. E.: Journ. of Ped. Vol. 12, 1938, p. 579. — 11. LAHDENSU, S.: Monatschr. f. Kinderheilk. 92, 1942, p. 340. — 12. DE LANGE, C. and WOLTRING, L.: Acta Pæd. XIX 1936, p. 71. — 13. DE LANGE, C., GERLINGS, P. G., DE KLEIN, A. and LETTINGA, T. W.: Acta Pæd. XXXI 1944, p. 398. — 14. LIEBENAM, L.: Zeitschr. f. Kinderheilk. LXI 1938, p. 91. — 15. LURIE, L. A. and LEVY, S.: Am. J. M. Sc. 207, feb. 1944, p. 184. Ref. Yearbook of Pediatrics 1944, p. 263. — 16. NIELSEN, H.: Forelæsninger over klinisk Endokrinologi og beslægtede Emner. Bd III. København 1942. — 17. REILLY, W. A.: Am. J. Dis. Child. Vol. 62, 1941, p. 489. — 18. ROSS, J. R., HAWKE, W. A. and BROWN, A.: Arch. Dis. Childh. Vol. 16, 1941, p. 71. — 19. SHELDON, W.: Proc. Roy. Soc. Med. 27, 1934, p. 1003. — 20. TUTHILL, C. R.: Arch. Neurol. 32, 1934, p. 198. — 21. WAARDENBURG, P. J.: Ophthalmologia, Vol. 99, 1940, p. 307.

Über das Vorkommen von schwachsinnigen Kindern verschiedener Typen und verschiedenen Alters sowie über ihre Möglichkeiten am Leben zu bleiben.

Von

N. HALLMAN.

Alle entweder seit ihrer Geburt oder seit dem frühen Kindesalter geistig minderwertigen Individuen nennen wir schwachsinnig (Oligophrenia). Im engeren, eigentlichen Sinne sind die Oligophrenen nach dem Grad des Defekts eingeteilt in die Debilen, die Imbezillen und die Idioten. Bezüglich ihrer Behandlung und teilweise ihrer Entwicklung kann man jedoch die Mikrocephalen, die Mongoloiden, die amaurotischen Idioten, die Wasserköpfe und einige andere seltenere Formen als Spezialgruppen der Schwachsinnigen auffassen, dessen ungeachtet, dass sie nach den neuesten Forschungen gesondert als Stoffwechsel — und »unter Irresein bei Hirnerkrankungen« — Gruppe zu behandeln wären (BUMKE). Zu bemerken ist jedoch, dass leichter Wasserkopf nicht immer unbedingt geistige Minderwertigkeit voraussetzt, was aber doch meistens der Fall ist.

Die Weltliteratur über die Schwachsinnigen ist ausserordentlich umfangreich. Der weitaus grösste Teil davon behandelt Individuen, welche das Säuglings- und Kleinkinderalter schon überschritten haben. Es ist auch natürlich, dass die Kinder in diesem Alter mehr Beachtung auf sich ziehen, indem sie ihr eigenes soziales Problem bilden. Es ist auch bekannt, dass die Entwicklung des Individuums in der früher Kindheit sehr verschieden sein kann. Die einen entwickeln sich schnell, während die Entwicklung bei anderen wiederum bedeutend langsamer vor sich

geht. Eine solche langsame Entwicklung kann in einer Familie auch erblich sein. Je jünger das Kind ist, um so schwerer lässt sich die Grenze zwischen normaler und unnormale langsamer Entwicklung ziehen. Natürlich gibt es viele auch für ein ungeübtes Auge klare Fälle, aber die Entwicklungsstufe, welche das Kind später erreichen wird, ist meistens äusserst schwer früh zu bestimmen.

In die Statistiken kommen die meisten Schwachsinnigen erst, nachdem sie das Schulalter erreicht haben. Im Hinblick auf soziale Verhältnisse haben sie auch erst dann Bedeutung, wenn die für Entwicklungsfähige notwendige Spezialschulung und die für Entwicklungsunfähige in den meisten Fällen unerlässliche Anstaltbehandlung zur Tagesordnung kommt. Wenn wir noch die allgemein bekannte grosse Sterblichkeit der Schwachsinnigen in den ersten Lebensjahren berücksichtigen, über welche meines Wissens jedoch nirgends besondere numerische Angaben gemacht worden sind, so bekommt man den Eindruck, dass die Anzahl der Schwachsinnigen, besonders im Vergleich zu allen Geborenen, grösser sei als die Statistiken zeigen.

Vom Standpunkt des Kinderarztes ist es sehr interessant, die späteren Schicksale der schon in der frühen Kindheit, mindestens vor dem Schulalter diagnostizierten Schwachsinnigen zu verfolgen. In nähere Berührung mit ihnen gerade in den ersten Lebensjahren kommen die Kinderärzte und Kinderkrankenhäuser. Später verschwinden diese Kinder wiederum oft aus dem Gesichtskreis. Wenn wir das Material des Kinderkrankenhauses einer Prüfung unterziehen, bekommen wir erstens einmal eine klarere Auffassung über die Mortalität dieser Kindergruppen und gleichzeitig auch ein gewisses Bild davon, wozu solche früh diagnostizierte Schwachsinnige später getaucht haben, mit anderen Worten, ein wie grosser Teil von ihnen eine Last für die Allgemeinheit geblieben ist, und wie viele durch den Tod ausgeschieden wurden.

I. *Material.*

Die Untersuchung umfasst alle in den Jahren 1909—1942 in der Kinderklinik der Universität Helsinki behandelten eigent-

lichen Schwachsinnigen, die Mikrocephalen, Mongoloiden, amaurotischen Idioten und Hydrocephalen. Die Resultate basieren auf Angaben, welche durch Versendung von Fragebogen an die nächsten Angehörigen erhalten wurden. Aus natürlichen Gründen kann ein Teil der Antworten subjektiv gegeben sein, denn es handelt sich ja um heikle Angelegenheiten. Ein zu schlechtes Bild von dem Material geben sie jedoch nicht. — Die Fragen sind möglichst einfach und schematisch gestellt worden.

II. *Über die Anzahl der Schwachsinnigen.*

Die Ziffern über die Anzahl der Schwachsinnigen in den verschiedenen Ländern sind recht verschieden. Die ältesten Mitteilungen stammen von KOLLMAN aus dem Jahre 1884, nach welchen in Preussen ein Schwachsinniger auf 730 Einwohner kam und entsprechend in England auf 771, in Frankreich auf 1028, in Schweden auf 2554 und in Belgien auf 2890 Einwohner. Die Zahlen aus den verschiedenen Ländern sind ganz offensichtlich zu schwankend um stichhaltig zu sein. Nach ZIEHEN gab es in Deutschland vor dem ersten Weltkriege ca. 1 % Schwachsinnige, und die neueren Berechnungen geben Zahlen von der gleichen Grössenklasse sowohl in Deutschland (STRECKER 1,6 % im Jahre 1936) als auch anderwärts in der Welt. v. BONSDORFF schätzte, dass es bei uns in Finnland um die Jahrhundertwende ca. 3,14 % Schwachsinnige gab. Nach einer im Jahre 1936 durchgeführten Untersuchung gibt es bei uns Idioten und Imbezillen insgesamt ca. 11 000 d. h. ca. 3 % von allen Einwohnern. Dazu kommen ausserdem noch die leicht Minderwertigen, die Debilen. Selbstverständlich variieren die Zahlen in den verschiedenen Statistiken je nachdem, welche Grenze zwischen normal und schwachsinnig gezogen wird.

Auch über die Kinder im Schulalter gibt es reichlich Mitteilungen. So wird z. B. aus der Schweiz im Jahre 1895 mitgeteilt, dass von den 7—14-jährigen Kindern 1,93 % schwachsinnig waren. KOLLER hat 9919 Schulkinder untersucht und unter ihnen 369 oder 3,7 % schlecht Entwickelte gefunden. DE VRIES und DE NEVE wiederum, erhielten in Leyden im Jahre 1918 von 30 000

unter 21-Jährigen 0,2 % (60) Idioten, 0,225 % (68) Imbezille und ausserdem 0,8 % Debile. In England wiederum (POTTS) wurde im Jahre 1923 geschätzt, dass von den 6—16-Jährigen ca. 30 000 geistig stark minderwertig waren, und ausserdem 106 000 kleinere Defekte hatten, insgesamt ca. 2 %. Aus Polen werden ca. 1 % der Schulkinder als schwachsinnig angegeben (WAWRZYŃSKI). — In den Hilfsklassen befanden sich (im Jahre 1891, BUMKE) in Hamburg 0,5 %, in Frankfurt a. M. 0,52 %, in Berlin 1,5 %, in Karlsruhe 0,78 % (DOLLINGER), in Meiningen 0,36 %. Nach späteren Mitteilungen gab es in Berlin 2 % Hilfsschüler und in Thüringen 2,2 % (BUMKE). Die von mir erwähnten Zahlen sind nur richtungsweisend angegeben. Nach v. BONSCHORFF hätte man bei uns in Finnland im Jahre 1915 850—900 Anstaltsplätze für entwicklungsfähige Idioten und Imbezille benötigt. Dazu kommen noch die ganz oder in hohem Masse Entwicklungsunfähigen hinzu.

Die oben angeführten Zahlen betreffen Schwachsinnige im Schulalter. Die jüngeren bleiben wahrscheinlich auch bei den das ganze Volk betreffenden Zahlen nur auf Schätzung angewiesen. Indem wir einige zur Verfügung stehende Zahlen aus Kinderkrankenhäusern prüfen, bekommen wir auch von dieser Altersklasse eine gewisse Auffassung. BLEYER hat in Amerika unter 50 000 poliklinisch behandelten Patienten, deren Alter von zwei Wochen bis 14 Jahre schwankte, 1,62 % schwachsinnige gefunden. Von diesen waren Mongoloiden 14,6 % oder 0,23 % des ganzen Materials. VAS hat aus einem ungarischen Poliklinik-Material entsprechend 0,22 % Schwachsinnige und davon Mongoloiden 22,8 % oder 0,05 % des ganzen Materials angetroffen. Der Schwede HELSTÉN hat in den Jahren 1923—32 im Kinderkrankenhaus von Lund sowohl das poliklinische als auch das klinische Material untersucht. Bei dem ersteren fand er Schwachsinnige 2,22 % und davon Mongolidioten 28,4 %, und als eigentliche Krankenhauspatienten waren 2,18 % Schwachsinnige behandelt worden, unter welchen die Mongolidioten 28,95 % ausmachten. Das Alter der Patienten schwankte von einigen Tagen bis zu 13 Jahren. Das poliklinische Material umfasste 5 900 und das klinische Material 6 957 Fälle. Ausserdem gibt es eine Reihe von Untersuchungen, welche besonders die Mongolidioten behandeln (s. LAHDENSUO),

aber schon die obigen Zahlen geben ein genügendes Bild vom Auftreten dieser Krankheit oder besser Entwicklungsstörung.

Wirkliche Mikrocephalen haben BRUSFIELD und WYATT unter 1545 Schwachsinnigen 70 oder also 4,46 % gefunden. — Über die Frequenz der amaurotischen Idiotie habe ich keine zahlenmässigen Angaben finden können, ebensowenig im Vergleich zu den eigentlichen Schwachsinnigen als auch anderen.

Die Hydrocephalen kann man den Obigen nicht direkt gleichstellen. Dennoch finden sich auch über ihre Frequenz keine numerischen Angaben.

Wenn wir die aus den Krankenhäusern erhaltenen Zahlen beispielsweise mit den bei Schulkindern ermittelten vergleichen, so lässt sich feststellen, dass sie ungefähr zur gleichen Grössenklasse gehören. Die Letzteren umfassen auf Grund des Schulzwanggesetzes die ganze Altersklasse, während zu den Ersteren nur diejenigen gehören, welche auf Veranlassung der Eltern in das Krankenhaus gebracht wurden. In den meisten Fällen ist die Ursache hierfür gerade die schlechte Entwicklung. Im Vergleich zur ganzen Altersklasse wirken diese Zahlen verhältnismässig gross. Andererseits ist zu berücksichtigen, dass die in der Entwicklung weniger Zurückgebliebenen sich durchaus nicht alle deshalb an den Arzt gewandt haben, sondern gerade die Hilfsklassen füllen, in welche die früh Diagnostizierten, sobald sie das Schulalter erreicht haben, selten gelangen.

In den Jahren 1909—1942 sind in der Kinderklinik der Universität Helsinki insgesamt 18 890 Patienten behandelt worden, deren Alter von einigen Tagen bis zu 14 Jahren variiert, jedoch so, dass diejenigen, welche das Schulalter noch nicht erreicht haben, die gewaltige Mehrheit ausmachen. Zu dieser Arbeit gehörige Diagnosen wurden folgendermassen gestellt:

Idiotia.....	134	0,70 %	
Imbecillitas.....	135	0,71 %	
Debilitas.....	42	0,22 %	1,63 %
Microcephalus.....	49	0,27 %	
Idiotia mong.....	100	0,54 %	
» amaur.....	30	0,17 %	2,59 %
Hydrocephalus.....	227	1,20 %	
Zusammen	717	3,79 %	

Eigentliche Schwachsinnigkeit kam also insgesamt 211 mal oder in 1,63 % von allen in dem Krankenhaus behandelten Patienten vor. Wenn wir noch die Mikrocephalen, die Mongoloiden und die amaurotischen Idioten berücksichtigen, können wir die erhaltene Zahl 2,59 % mit den oben erwähnten Untersuchungen vergleichen. Wir bemerken, dass in dem hiesigen Krankenhaus mehr schwachsinnige Kinder behandelt worden sind als HELLSTEN aus Lund mitteilt (2,18 %), ganz zu schweigen von den von BLEYER (1,62 %) und VAS (0,22 %) erhaltenen Zahlen. Auch der Anteil der Mongoloiden, 0,54 % von allen behandelten Fällen, ist grösser als die oben angeführten Zahlen der anderen Kliniken. — Nach verschiedenen Statistikern werden die Mongoloiden auf 1—10 % von allen Schwachsinnigen berechnet (LAHDENSUO). Bei uns ist die Zahl 20,41 %.

Die Mikrocephalen machen 10 % von allen Schwachsinnigen aus. Die Zahl ist fast doppelt so gross wie die von BRUSFIELD und WYATT gegebene, aber bei den Letzteren dürfte hinsichtlich der Grösse des Kopfes strengerer Masstab angelegt worden sein.

Unter der Diagnose *Idiotia amaurotica* sind 0,17 % von allen Patienten behandelt worden, und von den geistig Zurückgebliebenen gehörte jeder 16. oder 6,1 % in diese Klasse. Die Frequenz ist also verhältnismässig gross.

Auffallend ist die relativ grosse Anzahl der Hydrocephalen, nicht weniger als 1,20 % von allen in dem Krankenhaus behandelten Patienten. Die Krankheit ist jedoch in den meisten Fällen so deutlich festzustellen und die Symptome so alarmierend, dass sich in unserer Klinik, welche unter den wenigen Kinderkrankenhäusern in unserem Lande führend ist, ohne Zweifel im Vergleich zu den anderen relativ viele Fälle angesammelt haben. Schlussfolgerungen über die allgemeine Frequenz lassen sich auf Grund dessen also nicht ziehen.

Es sei noch erwähnt, dass nur 8,2 % von allen zu dem Material gehörigen Patienten über 7 Jahre alt, also schulpflichtig waren. 31,9 % waren 3—7 Jahre alt und der Rest, 59,9 %, unter 2 Jahren.

III. Geschlecht.

Nach den dieses Gebiet betreffenden Untersuchungen ist unter den Schwachsinnigen das Verhältnis der Knaben zu den Mädchen im allgemeinen 4:3 (BUMKE). Dies würde darauf beruhen, dass die schwerer zu erziehenden Knaben häufiger zur ärztlichen Behandlung oder in eine Anstalt kommen. Dagegen hat z. B. GODDARD keinerlei Unterschiede zwischen den beiden Geschlechtern beobachtet. — Idioten, Imbezillen und Debile sind in meinem Material insgesamt 175 Knaben und 136 Mädchen (Tabelle Nr. 1). Das Verhältnis ist etwas mehr als 4:3. Wenn das Ver

Tabelle Nr. 1.

Diagn. sis	Jahr		1—2 Jahre		2—7 Jahre		7 Jahre		Zusammen	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Idiotia	13	18	24	22	34	14	3	6	74	60
Imbecillitas . .	6	11	16	19	39	23	12	9	73	62
Debilitas . . .	6	4	4	2	11	3	7	5	28	14
Microcephalus	9	11	6	7	6	8	1	1	22	27
Idiotia mong.	28	38	5	9	8	11	0	1	41	59
» amaur.	4	1	6	7	3	8	0	1	13	17
Hydrocephalus	68	63	20	15	28	22	8	3	124	103

hältnis nach Altersklassen betrachten, so lässt sich feststellen, dass es bei den unter 2-Jährigen umgekehrt ist. Mädchen gibt es 76, aber Knaben nur 69. Dieser Umstand dürfte als ein gewisser Beweis für die Erziehungstheorie aufgefasst werden können. In diesem Alter dürfte in der Erziehung der beiden Geschlechter noch kein grösserer Unterschied bestehen.

Nach ROSANOFF und HANDY befinden sich auch unter den Mongoloiden mehr Knaben als Mädchen. Nach zahlreichen anderen Autoren gibt es jedoch keinen Unterschied (LAHDENSUO). Merkwürdigerweise enthält mein Material 59 Mädchen und Knaben wiederum nur 41. Der Unterschied ist zwar ganz deutlich, aber da das ganze Material nur 100 Fälle umfasst, ist das Resultat

tat eher als ein Gegengewicht zu der Mitteilung von ROSANOFF und HANDY und als ein Beweis dafür anzusehen, dass zwischen den beiden Geschlechtern in dieser Hinsicht kein nennenswerter Unterschied besteht.

Von den Mikrocephalen sind 27 Mädchen und 22 Knaben. Von den amaurotischen Idioten entsprechend 17 und 13. Über grössere Unterschiede zwischen den Geschlechtern finden sich in der Literatur keine Angaben. Auch jetzt handelt es sich um eine so kleine Anzahl Patienten, dass man keine klaren Schlussfolgerungen ziehen kann, obwohl in beiden verhältnismässig mehr Feminine vorkommen.

Von den Hydrocephalen sind 103 Mädchen und 124 Knaben. Über grössere Unterschiede ist auch von diesen früher nichts erwähnt wurden.

IV. Sterblichkeit.

Die Sterblichkeit des ganzen untersuchten Materials geht aus *Tabelle Nr. 2* hervor. Antworten auf die Erkundigungen wurden

Tabelle Nr. 2.

Diagnosis	Behandelte Fälle insgesamt	Gestorben	%
Idiotia	91	50 (3)	54,9
Imbecillitas	82	22	26,8
Debilitas	22	9	40,9
Microcephalus	30	15	50,0
Idiotia mong.	70	53 (13)	75,7
» amaur.	18	10	55,6
Hydrocephalus	147	102 (30)	69,4
Zusammen	460	266 (46)	57,8

In Klammern im Krankenhaus gestorbene Patienten.

in 460 Fällen von 717, also in 64,2 % erhalten. Davon waren 261 oder 58,7 % gestorben. Die höchsten Mortalität trat bei den Mongoloiden auf, nämlich 75,7 %. Darauf folgten die Wasserköpfe mit 69,4 % und dann die anderen Typen mit schon bedeutend klei-

neren Zahlen. Bei den Imbezillen war die Sterblichkeit am niedrigsten (26,8 %). Während des Aufenthalts im Krankenhaus waren insgesamt 46 gestorben, und von diesen war der grösste Teil Hydrocephalen, welche mit aktiven Massnahmen behandelt worden waren, sowie Mongoloiden, von welchen wiederum der grösste Teil an Infektionen der Respirationswege gestorben war. Im folgenden wird die Mortalität der verschiedenen Gruppen etwas näher betrachtet.

A. Die eigentlichen Schwachsinnigen.

Es ist eine allgemein bekannte Tatsache, dass die Schwachsinnigen jung sterben. Zahlenmässige Angaben über ihre Sterblichkeit im frühen Kindesalter habe ich, wie oben schon erwähnt, nicht gefunden.

Wenn wir zunächst die Totalsterblichkeit der Idioten, Imbezillen und Debilen betrachten, so würde man erwarten, dass das Mortalitätsprozent, weil ja auch die ältesten Fälle von ihnen noch nicht einmal ordentlich die mittleren Jahre erreicht haben, bei den Idioten am grössten wäre und bei den Debilen am kleinsten. Je grösser der Mangel an Intelligenz ist, für umso schwächer möchte man auch die Entwicklung des übrigen Organismus halten. Aus *Tabelle Nr. 2* ist ersichtlich, dass die Sterblichkeit unter den Idioten am grössten ist, aber bei den allerleichtesten Fällen dagegen, den Debilen, ist sie deutlich grösser als bei den Imbezillen. Auf diesen Umstand werde ich noch später zurückkommen.

Der verhältnismässig grösste Teil von den gestorbenen Schwachsinnigen (Idioten 80 %, Imbezille 63,5 % und Debile 77, 8 %) starb ehe er das Schulalter erreicht hatte (*Tabelle Nr. 3*). Wir bekommen jedoch von der Sterblichkeit der verschiedenen Altersklassen gewissermassen ein falsches Bild, denn die verschiedenen Fälle kamen durchaus nicht im gleichen Alter zur Observation. Wir können unmöglich gleich nach der Geburt alle Schwachsinnigen absondern und dann die Mortalität dieser Gruppe verfolgen schon deshalb, weil sich der Mangel an Verstand selten sehr frühe herausstellt. Oft bemerken die Eltern die schlechte Entwicklung erst in einem Alter, wo die Kinder anfangen sollten

Tabelle Nr. 3. Sterbealter berechnet in % von allen Gestorbenen.

Diagnosis	—1 Jahr	1—2 Jahre	2—7 Jahre	7—10 Jahre	10—20 Jahre	20— Jahre
Idiotia	10,0	22,0	48,0	6,0	10,0	4,0
Imbecillitas .	9,1	18,2	36,2	13,6	22,6	0
Debilitas . . .	22,2	33,3	22,2	22,2	0	0
Microcephalus	13,3	13,3	53,2	6,7	6,7	6,7
Idiotia mong.	54,7	20,8	7,6	11,3	5,6	0
» amaaur.	0	10,0	70,0	0	10,0	10,0
Hydrocephalus	63,9	17,5	5,2	7,2	6,2	0

Tabelle Nr. 4.

Alter beim Eintreffen im Krankenhaus	Fälle insge- samt	Ge- storbene ins- gesamt	S t e r b e a l t e r					
			—1 Jahr	1—2 Jahre	2—7 Jahre	7—10 Jahre	10—20 Jahre	20— Jahre
		%	%	%	%	%	%	%
— $\frac{1}{2}$ Jahr	11	9 81,2	3 27,3	4 36,5	2 18,2	0 0	0 0	0 0
$\frac{1}{2}$ —1 »	23	18 78,1	6 26,1	6 26,1	4 17,4	2 8,7	0 0	0 0
1—2 Jahre	59	26 44,1	— —	8 13,6	15 25,4	0 0	1 1,8	2 3,5
2—7 »	76	25 32,9	— —	— —	13 17,1	5 6,6	7 9,1	0 0
7— »	26	3 11,6	— —	— —	— —	1 3,5	2 6,9	0 0

zu sitzen, zu gehen, zu sprechen usw., in leichteren Fällen entsprechend noch später. Der Gegensatz zwischen dem eigenen, als ein artiges Musterkind betrachteten und den anderen Kindern tritt jetzt erst in Erscheinung. Andererseits befinden sich in der verhältnismässig grossen Gruppe der früh gestorbenen Lebensschwachen sicherlich auch reichlich Schwachsinnige, welche nicht diagnostiziert werden.

Es ist die allgemeine Regel, dass die Prognose umso schlechter ist, je früher die Schwachsinnigkeit festgestellt wird. Wenn wir die in bestimmtem Alter zur Behandlung gekommenen Patienten (Idiotia + Imbecillitas + Debilitas) betrachten (Tabelle Nr. 4), können wir den gleichen Schluss ziehen. Von denjenigen, welche

jünger als $\frac{1}{2}$ -jährig ins Krankenhaus gekommen waren (11), sind insgesamt 9 oder 81,2 % bis jetzt gestorben, und zwar alle, ehe sie das Schulalter erreicht hatten. Die Lebenden sind beide über 10-jährig. Im Alter von $\frac{1}{2}$ —1 Jahr kamen 23 zur Behandlung, und von diesen 18 oder 78,1 % gestorben. Auch von diesen erreichten nur zwei das Schulalter, aber auch diese starben unter 10 Jahren. Von den am Leben Gebliebenen sind noch zwei unter dem Schulalter, einer ausserdem unter 10-jährig, und zwei über 10-jährig. *Wenn wir alle im Alter von unter 1 Jahr Diagnostizierten berücksichtigen, erhalten wir für die Sterblichkeit vor dem ersten Lebensjahr 26,5 % und vor dem Schulalter 73,6 %.* — Ganz deutlich kleiner ist die Sterblichkeit schon in der Gruppe derjenigen, welche unter 2-jährig zur Behandlung gekommen sind, aber doch über 1 Jahr. Von 59 sind nur 26 oder 44,1 % gestorben, und von diesen zwei im Alter von über 20 Jahren. Weitaus am grössten war die Sterblichkeit auch bei diesen in den ersten Jahren nach der Feststellung der Krankheit, indem sie bis zum Schulalter 39 % und danach also nur 5,1 % betrug. Von den Lebenden sind 2 über 20 Jahre alt, 8 10—20 Jahre, und 15 7—10 Jahre. — Wenn wir weiterhin zu den noch älter ins Krankenhaus Gekommenen übergehen, stellen wir fest, dass von denjenigen, welche im Alter von 3—7 Jahren zur Behandlung kamen, nur 32,9 % gestorben sind. *Wenn wir alle im Alter von unter 7 Jahren Gekommenen berücksichtigen, ist die Mortalität 46,2 % gewesen und vor dem 7. Lebensjahr 36,1 %.* Es sei noch erwähnt, dass von denjenigen, welche über 7-jährig zur Behandlung kamen, nur 3 oder 11,6 % gestorben sind. Zwischen dem Alter, in welchem die Krankheit festgestellt wurde, und der Sterblichkeit besteht also ein klares Verhältnis. *Je früher die Krankheit festgestellt wird, um so grösser ist die Sterblichkeit in den ersten Jahren nach der Diagnostizierung.* Fig. Nr. 1 gibt ein klares Bild von der Mortalität vor dem Schulalter. Wenn wir die allgemeine Sterblichkeit der verschiedenen Altersklassen in den ersten Lebensjahren bedenken, so ist sie gewaltig viel kleiner als bei den Schwachsinnigen.

Es ist noch zu erwähnen, dass von den gestorbenen Schwachsinnigen einer Spina bifida hatte, einer Myatonia congenita, zwei Hypofunktion der Schilddrüse, einer Epilepsie, einer war taub-

stumm und einer hatte Morbus Little. Von den am Leben Gebliebenen wiederum hat einer Myatonia congenita, 2 Hypothyreosis, 7 Epilepsie, 4 sind taubstumm und einer hat Morbus Little.

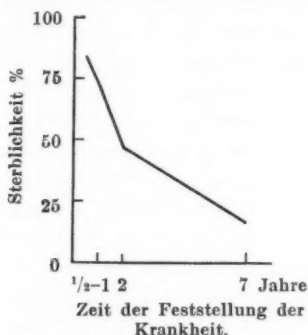


Fig. Nr. 1. Sterblichkeit vor dem Schulalter.

Als Todesursache wurde angegeben:

Fieberkrankheit.....	20	Krämpfe.....	10
Lungenentzündung.....	16	Lähmung.....	1
Gehirnhautentzündung.....	6	Hirntumor.....	2
Tuberkulose.....	2	Unfall.....	1
Entkräftung.....	13	Unbekannt.....	8

Der grösste Teil ist also an verschiedenen Infektionskrankheiten gestorben, von welchen die Lungenentzündung die Hauptrolle spielt. Verhältnismässig viele sind auch an verschiedenen Symptomen des Zentralnervensystems gestorben. Zu beachten ist, dass bei zweien als Todesursache ein Hirntumor angegeben wurde.

B. *Microcephalus*.

Von den in Behandlung gewesenen Mikrocephalen, von welchen nähere Angaben erhalten wurden, ist genau die Hälfte gestorben. Das Material ist so klein (30), dass man keine sicheren Schlussfolgerungen ziehen kann. Die 15 Gestorbenen verteilen sich auf

Tabelle Nr. 5.

Alter beim Eintreffen im Krankenhaus	Fälle insgesamt	Gestorbene insgesamt	Sterbealter					
			—1 Jahr	1—2 Jahre	2—7 Jahre	7—10 Jahre	10—20 Jahre	20— Jahre
		%	%	%	%	%	%	%
— $\frac{1}{2}$ Jahr	4	2 50,0	1 25,0	0 0	1 25,0	0 0	0 0	0 0
$\frac{1}{2}$ —1 »	7	4 57,1	1 14,3	0 0	3 42,8	0 0	0 0	0 0
1—2 Jahre	8	4 50,0	— —	2 25,0	2 25,0	0 0	0 0	0 0
2—7 »	10	5 50,0	— —	— —	2 20,0	1 10,0	1 10,0	1 10,0
7— »	1	0 0	— —	— —	— —	0 0	0 0	0 0

die verschiedenen Altersklassen ungefähr gleichmässig (Tabelle Nr. 5). Von denjenigen, welche unter dem Schulalter zur Behandlung gekommen waren, starben 41,4 % vor dem vollendeten 7. Lebensjahr. Die Zahl gehört zur gleichen Grössenklasse wie die den eigentlichen Schwachsinnigen entsprechende. Zu beachten ist, dass die Sterblichkeit bei den jünger ins Krankenhaus Gekommenen nicht grösser ist als auch bei den übrigen. Nur bei zweien war das Schulalter über 10 Jahre. Von den noch Lebenden sind nicht weniger als 12 noch unter 10-jährig und die restlichen drei unter 20-jährig. — Von den Gestorbenen hatten zwei Morbus Little.

Die Todesursachen waren folgende:

Lungenentzündung.....	5	Atmungslähmung.....	1
Fieberkrankheit.....	5	Unbekannt.....	2
Krämpfe.....	2		

Auffallend ist auch hier der relativ grosse Anteil der Infektionskrankheiten.

C. *Idiotia mongolidea*.

In der Literatur gibt es reichlich Untersuchungen über diesen verhältnismässig spät dargestellten Typus. Man weiss, dass ihre Lebenszeit sehr kurz ist, und dass sie nur selten die mittleren Jahre erreichen. In den verschiedenen Untersuchungen variiert

das Lebensalter, wobei es sich 10 Jahren nähert (genauer s. LAHDENSUU). — Beim grössten Teil der Mongoloiden dieses Materials ist das Sterbealter unter 2 Jahre (*Tabelle Nr. 3*). Wenn wir die in verschiedenem Alter zur Behandlung Gekommenen berücksichtigen (*Tabelle Nr. 6*), wächst die Sterblichkeit der ersten

Tabelle Nr. 6.

Alter beim Eintreffen im Krankenhaus	Fälle insgesamt	Gestorbene insgesamt	Sterbealter					
			—1 Jahr	1—2 Jahre	2—7 Jahre	7—10 Jahre	10—20 Jahre	20— Jahre
		%	%	%	%	%	%	%
— $\frac{1}{2}$ Jahr	31	27 87,1	24 77,4	3 9,7	0 0	0 0	0 0	0 0
$\frac{1}{2}$ —1 »	12	8 66,7	5 41,7	3 25,0	0 0	0 0	0 0	0 0
1—2 Jahre	14	10 71,4	— —	5 35,8	1 7,2	3 21,4	1 7,2	0 0
2—7 »	8	6 75,0	— —	— —	3 37,5	3 37,5	0 0	0 0
7— »	5	2 40,0	— —	— —	— —	0 0	2 40,0	0 0

Lebensjähre. So starben von den 43, welche im Alter von unter 1 Jahr zur Behandlung kamen, 29 oder 67,5 %, ehe sie diese Altersgrenze erreicht hatten. Bis zum Schulalter starben von diesen ausserdem noch 6 oder also 81,4 % im ganzen. Diese Zahl entspricht ungefähr den von STEIN mitgeteilten 87 % vor dem Schulalter. Wenn wir nur die unter $\frac{1}{2}$ -jährig zur Behandlung Gekommenen berücksichtigen, kommen wir dieser Zahl noch näher. Bei denjenigen, welche erst älter ins Krankenhaus kamen, war die Lebenszeit länger wie aus der Tabelle hervorgeht. Trotzdem starben insgesamt nur 9 im Alter von über 7 Jahren. Von den am Leben Gebliebenen ist 1 über 20 Jahre alt, 6 zwischen 10 und 20 Jahren, 8 zwischen 7 und 10 Jahren und 2 unter 7 Jahren. Von den jetzt Lebenden hat kein einziger angeborenen Herzfehler, während ein solcher bei den Gestorbenen dagegen 9 mal festgestellt wurde. Alle diese starben im Verlauf des ersten Lebensjahrs. Es sei noch erwähnt, dass von den jetzt Lebenden einer taubstumm ist, einer hat seit der Geburt Star, und zwei leiden an einer Krampfkrankheit (Epilepsie?).

Die Todesursachen waren folgende:

Lungenentzündung.....	24	Entkräftung.....	7
Fieberkrankheit.....	8	Herzschwäche.....	7
Gehirnhautentzündung.....	1	Anus-Atresie.....	1
		Unbekannt.....	5

Der grösste Teil starb also an Infektionskrankheiten. Schon früher ist ihre geringe Widerstandsfähigkeit gegen verschiedene Infektionskrankheiten und besonders gegen Lungenentzündung festgestellt worden.

D. *Idiotia amaurotica.*

Von der amaurotischen Idiotie gibt es Kindheits- und Jugendformen. Die erstere beginnt schon im Alter von $1\frac{1}{2}$ —3 Jahren, die letztere wiederum etwas später. Die erstere führt schon in einigen Jahren durch Blindheit und allgemeine Verblödung zum Tod. Die letztere kann längere Zeit dauern, aber auch dann ist rettungslos der gleiche Tod die Folge. — Von den 18 Fällen dieses Materials sind 10 als gestorben gemeldet worden (55,6 %). Von diesen war einer über 20 und einer über 10 Jahre alt, alle übrigen jünger. Von den jetzt Lebenden sind drei unter 5 Jahre alt, aber einer über 20 Jahre. — Die Todesursache war bei einem Gehirnhautentzündung und bei 2 eine Fieberkrankheit. Die restlichen 5 gingen allmählich zugrunde, wie es zu dem Krankheitsbild gehört.

E. *Hydrocephalus.*

Über 147 von den 227 Fällen des Materials wurden Angaben erhalten. Bezüglich ihrer Ätiologie und verschiedenen Prognose können wir sie in drei Gruppen einteilen: 1. Hydrocephalus cong. 2. Hydrocepyalus cong. und ausserdem noch ein anderer Entwicklungsfehler in den Gehirnhäuten. 3. Hydrocephalus aquisitus.

1. Die eigentlichen angeborenen Wasserköpfe können wir weiterhin in äussere und innere einteilen. Von den ersteren gehören zu diesem Material nur 4, und von diesen erhielten wir Mitteilung nur über einen, der im Alter von unter 1 Jahr an einer Fieberkrankheit gestorben war. Die Gruppe der inneren Wasser-

Tabelle Nr. 7.

Alter beim Eintreffen im Krankenhaus	Fälle insgesamt	Gestorbene insgesamt	Sterbealter					
			—1 Jahr	1—2 Jahre	2—7 Jahre	7—10 Jahre	10—20 Jahre	20— Jahre
		%	%	%	%	%	%	%
— $\frac{1}{2}$ Jahr	48	40 83,3	35 72,9	4 8,3	1 2,1	0 0	0 0	0 0
$\frac{1}{2}$ —1 »	12	9 75,0	9 75,0	0 0	0 0	0 0	0 0	0 0
1—2 Jahre	24	12 50,0	— —	9 37,5	2 8,3	1 4,2	0 0	0 0
2—7 »	20	15 51,7	— —	— —	2 6,0	4 13,8	4 13,8	5 17,1
7— »	6	2 33,3	— —	— —	— —	1 16,6	1 16,6	0 0

köpfe ist gross, nämlich 176 Fälle, von welchen über 119 Mitteilungen erhalten wurden. Von diesen sind insgesamt 78 gestorben. Von den 60 Patienten, welche im Alter von unter 1 Jahr zur Behandlung kamen, sind 49 oder 81,7 % gestorben (Tabelle Nr. 7) und zwar alle vor dem 7. Lebensjahr. Nicht weniger als 73,3 % starben, ehe sie das erste Lebensjahr vollendet hatten. Von denjenigen, welche älter ins Krankenhaus kamen, blieb ein immer grösserer Teil am Leben. Wenn wir wiederum diejenigen nehmen, welche im Alter von unter $\frac{1}{2}$ Jahr kamen, so ist die Mortalität entsprechend grösser. Die grosse Sterblichkeit im ersten Lebensjahr ist eine altbekannte Tatsache (PAKUNKER, MISCH). Verhältnismässig gross ist die Sterblichkeit in den nächsten Jahren auch bei den älter zur Behandlung gekommenen Fällen. Von allen denjenigen, die unter dem Schulalter ins Krankenhaus kamen, starben vor dem 7. Lebensjahr 54,9 %.

Die Todesursachen waren folgende:

Hydrocephalus	41	Krämpfe	8
Fieberkrankheiten	12	Operation	4
Entkräftung	10	Gehirnhautentzündung . .	3

Es sei noch erwähnt, dass teils mit Hilfe der Lumbalpunktion teils der Obduktion bei 6 gestorbenen Patienten festgestellt wurde, dass der Wasserkopf durch ein Geburtstrauma erzeugt war. Eigentlich gehören diese in die dritte Gruppe. — Von den gegen-

wärtig Lebenden sind 5 über 20-jährig, 15 10—20-jährig, 8 7—10-jährig und 13 unter 7-jährig.

2. Verschiedene Missbildungen in den Gehirnhäuten hatten 21 Fälle. Davon hatten Encephalocle 2, von welchen der eine unter $\frac{1}{2}$ Jahr und der andere unter 2 Jahren starb. — Meningomyelocle hatten 8. Von diesen starben 6 im Alter von unter 1 Jahr, einer wurde nahezu 10 Jahre alt, aber über den achten liegen keine Angaben vor. Bei zwei von den erstgenannten wurde Operation versucht, aber mit schlechtem Resultat. — Spina bifida hatten 11, von welchen alle 6, über welche Angaben erhalten wurden, sogar schon im Alter von unter $\frac{1}{2}$ Jahr gestorben waren. Auch von diesen wurde bei einem Operation versucht mit dem gleichen Resultat wie oben.

3. Infolge von Gehirnhautentzündung bekamen 29 Kinder Wasserkopf, aller unter 2 Jahren. Von den 15, über welche Angaben erhalten wurden, waren 10 im Verlauf des nächsten Jahrs gestorben. Von diesen starben vier unter Meningitis-Symptomen und einer beim Versuch einer Gehirnoperation.

V. Über die spätere Entwicklung.

A. Die eigentlichen Schwachsinnigen.

Nach der allgemeinen Auffassung ist die Prognose der Schwachsinnigen umso schlechter, in je jüngerem Alter die Krankheit in Erscheinung tritt (BUMKE). Oben haben wir gesehen, wie auch in diesem Material die Sterblichkeit entsprechend schon in der sehr frühen Kindheit grösser ist. Im Folgenden soll untersucht werden, welche Entwicklungsstufe die bei uns behandelten Schwachsinnigen zu erreichen imstande gewesen sind.

Antworten betreffend Idioten, Imbezille und Debile kamen insgesamt 195, und von diesen sind gegenwärtig 114 am Leben. Wenn wir ausserdem denjenigen Teil der schon Gestorbenen berücksichtigen, über deren Entwicklungsstufe wir nähere Angaben erhalten haben, so bekommen wir als Gesamtsumme 174. In *Tabelle Nr. 8* sehen wir die Entwicklungsstufe dieses Materials altersklassenweise, nach der Diagnose eingeteilt. Wenn wir zu-

nächst die schon Gestorbenen berücksichtigen (in der Tabelle Zahlen in Klammern), so lässt sich feststellen, dass der grösste Teil auf niedriger Entwicklungsstufe stehengeblieben ist. Von 60 sind nicht weniger als 45 praktisch genommen apathisch, unfähig sowohl zu sprechen als auch zu gehen. Der grösste Teil von diesen starb, wie schon aus dem Obigen hervorgeht, sehr jung, aber das Schulalter erreichten immerhin 8. Keiner von diesen entwickelte sich soweit, dass er schultauglich gewesen wäre, aber 7 lernten allerdings sprechen und gehen. Von den jünger Gestorbenen hatten es ausserdem 4 soweit gebracht. — Es fällt auf, dass sowohl von Idioten, Imbezillen und Debilen verschiedene Entwicklungsstufe erreicht wurden. Verhältnismässig weniger haben zwar die Idioten sprechen und gehen gelernt, nämlich 10,2 %, während dies bei den Imbezillen wiederum in 37,5 % und bei den Debilen in 20 % der Fall war. Der Verteilung der späteren Jahre auf die Idioten, Imbezillen und Debilen entspricht das Resultat jedoch nicht. Auf jeden Fall hat der Tod gerade unter den am schlechtesten entwickelten Individuen die grösste Ernte gehalten.

Aus natürlichen Gründen ist von den gegenwärtig Lebenden ein viel grösserer Teil entwicklungsfähig gewesen. — Insgesamt wurden von diesen Antworten erhalten bei 41 mit der Diagnose Idiotia, 60 mit der Diagnose Imbecillitas und 13 mit der Diagnose Debilitas Behandelten. Von der mittleren, der *Imbecillitas-Gruppe*, waren nicht weniger als 3 oder 5 % zu Leistungen fähig, welche das Pensum der Volksschule überschritten, und die Volksschule hatten ausserdem 12 oder 20 % besucht. Im ganzen war also genau $\frac{1}{4}$ imstande gewesen, Schulstudien zu treiben. Von der *Debilitas-Gruppe* waren 5 oder 38,5 % für die Schule befähigt, von den Idioten dagegen kein einziger. — Sprechen und gehen lernten von den Idioten 46,3 %, von den Imbezillen ausser den oben erwähnten Schulfähigen 46,7 % und von den Debilen 38,5 %. Unfähig sowohl zu sprechen als auch zu gehen waren von der ersten Gruppe 23,9 %, von der zweiten 8,3 % und von der dritten kein einziger. Der Rest gehört in die Gruppe, welche wohl gehen gelernt haben, aber nicht sprechen können. Ausserdem waren darunter ein Idiot und 2 Imbezillen, die einige Wörter sprechen, aber nicht gehen können. Von diesen leiden zwei an Morbus Little. —

Krämpfe, am ehesten Epilepsie, bekamen früher oder später 13, davon 3 Imbezille, 1 Debiler und der Rest Idioten. Morbus Little hatten ausser den oben erwähnten zum Gehen unfähigen Fällen 6, und zwar ebensoviel Idioten wie Imbezillen. Schulfähig war von den Epileptikern einer, von den an M. Little Leidenden kein einziger. Ein für die Volksschule unbefähigter Fall bekam bei dem Aufenthalt im Krankenhaus die Diagnose Myxoedema. Taubstumme waren darunter 4, von welchen einer imstande war, erfolgreich die Taubstummenschule zu besuchen (Imbecillitas). Die restlichen drei wurden zur Gruppe der zur Volksschule Unfähigen gerechnet. Auch von diesen hatten zwei mit der Taubstummenschule angefangen, waren aber gezwungen gewesen, ihre Studien aufzugeben. In den Irrenanstalten sind gegenwärtig oder waren früher 3, sowie in den Pflegeanstalten für entwicklungsunfähige Schwachsinnige 8.

Es ist besonders interessant, die Entwicklung derjenigen Schwachsinnigen zu verfolgen, bei welchen die Diagnose in möglichst frühem Stadium gestellt wurde. Hierüber erhalten wir ein Bild aus Tabelle Nr. 9, wo die Entwicklungsstufe als Funktion des Alters beim Eintreffen im Krankenhaus angegeben ist.

Von denjenigen, welche unter $\frac{1}{2}$ Jahr zur Behandlung kamen, sind 2 am Leben, der eine ein Idiot, und der andere kam mit der Diagnose Debilitas. Aus Tabelle Nr. 10 ist ersichtlich, dass beide nunmehr im Alter zwischen 10 und 20 Jahren stehen. Der erstere ist unfähig sowohl zu sprechen als auch sich zu bewegen, der letztere kann sich zwar bewegen, aber nicht sprechen. *Alle im Alter von unter $\frac{1}{2}$ Jahr in das Krankenhaus gekommenen und dann diagnostizierten Schwachsinnigen sind also vollkommen unbrauchbare Individuen gewesen. Der grösste Teil von ihnen starb, ehe er das Schulalter erreicht hatte, und die übrigen sind völlig unfähig, selbständig zurechtzukommen.*

Von den 23, welche ausser den Obigen im Alter von unter einem Jahr zur Behandlung kamen, sind 5 am Leben. Von diesen haben zwei das Schulalter noch nicht erreicht, einer steht gerade in diesem Alter und zwei haben das 20. Lebensjahr noch nicht vollendet. Einer, welche mit der Diagnose Imbecillitas kam, kann weder sprechen noch gehen, 1 mit der Diagnose Idiotia eingetroffener,

Tabelle Nr. 9.

(Idiotia = I., Imbecillitas = Im., Debilitas = D.)

Alter beim Eintreffen im Krankenhaus	Spricht nicht Gehtnicht		Spricht nicht Geht		Spricht Gehtnicht		Unfähig für d. Volksschule		Hat d. Volksschule absolviert		Weitere Studien	
	I.	Im. D.	I.	Im. D.	I.	Im. D.	I.	Im. D.	I.	Im. D.	I.	Im. D.
— $\frac{1}{2}$ Jahr	1	0	0	0	0	1	0	0	0	0	0	0
$\frac{1}{2}$ —1 »	0	1	0	0	0	0	1	2	0	0	0	0
1—2 Jahre	4	4	0	3	4	1	0	1	0	5	9	0
2—7 »	4	0	0	7	5	1	0	0	0	9	12	2
7—10 »	1	0	0	1	1	0	0	1	0	2	2	2
10— »	0	0	0	0	0	0	0	2	3	1	0	0

Tabelle Nr. 10.

(Idiotia = I., Imbecillitas = Im., Debilitas = D.)

Alter z. Zt. d. Nachfrage	Alter beim Eintreffen im Krankenhaus				
	— $\frac{1}{2}$ Jahr	$\frac{1}{2}$ —1 Jahr	1—2 Jahre	2—7 Jahre	7— Jahre
	I. Im. D.	I. Im. D.	I. Im. D.	I. Im. D.	I. Im. D.
— 7 Jahre	0 0 0	1 1 0	4 5 1	0 0 0	0 0 0
7—10 »	0 0 0	1 0 0	6 9 0	6 9 2	0 0 0
10—20 »	1 0 1	0 2 0	2 6 2	13 11 1	6 8 4
20— »	0 0 0	0 0 0	0 0 0	1 6 2	0 3 2

an M. Little leidender Fall ist bewegungsunfähig, und die übrigen, 1 Idiot und 2 Imbezillen, waren unfähig, die Volksschule zu absolvieren. Auch diese *im Alter von unter 1 Jahr zur Behandlung gekommen waren also alle für das Gemeinwesen unbrauchbare Individuen.*

Von den 59 Fällen, welche im Alter von 1—2 Jahren diagnostiziert wurden, sind 33 am Leben. Die Volksschule konnten 3 besuchen, welche mit der Diagnose Imbecillitas behandelt worden waren. 5 Idioten und 9 Imbecillen lernten sprechen und gehen, und die restlichen 7 Idioten, 9 Imbezillen und 1 Debiler blieben

auf noch niedrigerer Stufe. Von allen behandelten Fällen waren also nur 5,4 % fähig, die Volksschule zu besuchen. Ausserdem ist noch zu bedenken, dass 5 das Schulalter noch nicht erreicht haben. Alle sind jedoch im Vergleich zu ihren Altersgenossen in der Entwicklung beträchtlich zurückgeblieben.

Sehr interessant ist, von diesen früh diagnostizierten Fällen die in der Entwicklung weitergekommenen Patienten zu verfolgen. Bei zwei von ihnen handelte es sich ausser der geistigen Minderwertigkeit noch um eine Infektionskrankheit (Dyspepsia chron. p. t. ac., Infectio ac.), welche längere Zeit dauerte und das Allgemeinbefinden herabsetzte. Zweifelsohne wirkte sie hemmend und teilweise rückschrittlich sowohl auf die körperliche als auch auf die geistige Entwicklung, was in der Anamnese deutlich hervortritt. Später, als die Infektion schon geheilt war, wurde die Entwicklung lebhafter, und die Eltern sind der Ansicht, dass sie sich in ihrer gegenwärtigen Entwicklung nicht von ihren Altersgenossen unterscheiden. Der Andere, welcher die Volksschule und ausserdem 5 Klassen der Mittelschule absolviert hat, leidet zwar an irgendwelcher psychischen Empfindsamkeit, wofür die vom Arzt festgestellten Minderwertigkeitskomplexe ein Beweis sind. — Der dritte Patient hatte starke Rachitis, welche ohne Zweifel seinerzeit verzögernd wenigstens auf die körperliche Entwicklung eingewirkt hat. Einfluss auf die spätere Intelligenz hat die Rachitis nicht, wie BRANDEE nachgewiesen hat. Eine gewisse Minderwertigkeit hat indessen auch dieses Individuum. Dies beweisen die »Wachträume«, die der Patient haben soll. — Obwohl man auf Grund der erhaltenen Angaben die gegenwärtige Entwicklungsstufe der Patienten nicht exakt beurteilen kann, weil die Subjektivität der Angehörigen, welche die Angaben gemacht haben, auf diese einwirken konnten, und weil die Absolvierung der Volksschule an sich kein zuverlässiger Mastab ist, so bekommt man doch den Eindruck, als ob bei der Stellung der Diagnose zu weitgehende Schlussfolgerungen gezogen worden wären. Dies dürfte am ehesten auf der Wirkung der gleichzeitig aufgetretenen Infektionskrankheiten und der Rachitis beruhen. Der kurze Aufenthalt im Krankenhaus macht die Beurteilung ebenfalls ausserordentlich schwierig.

Von denjenigen, welche unter dem Schulalter aber doch über 2-jährig zur Behandlung kamen (76), hat sich ein immer grösserer Teil besser entwickelt. Auch die Sterblichkeit ist, wie oben schon erwähnt, unter diesen kleiner als bei den früher Gekommenen. Die Volksschule haben 7 mit der Diagnose Imbecillitas Behandelte besucht und entsprechend 2 von den Deбилen. Als Prozentzahl erhalten wir 12. Sprechen und gehen haben ausserdem 23 von den Patienten gelernt, so dass es schwächer entwickelte also insgesamt 17 gibt.

Obwohl man, wie gesagt, auf Grund der Antworten kein unbedingt zuverlässiges Bild von der gegenwärtigen Entwicklungsstufe der Behandelten erhält, so dürfte es doch angebracht sein, auch von dieser Gruppe wenigstens diejenigen kurz durchzugehen, welche imstande waren, die Volksschule zu besuchen.

Vier von den erwähnten Fällen kamen im Alter von unter 3 Jahren zur Behandlung. Drei hatten ausser der diagnostizierten Schwachsinnigkeit noch eine Infektionskrankheit (*Infectio ac.*, Influenza, *Dyspepsia*), derentwegen sie in erster Linie ins Krankenhaus kamen. Die zwei zuletzt erwähnten haben nach Aussage der Eltern keinen geistigen Defekt mehr. Es ist jedoch zu berücksichtigen, dass sie gegenwärtig ihrem Alter gemäss erst die Volksschule besuchen. Der dritte sowie der letzte in dieser Gruppe, welche beide schon körperlich Zeichen der Schwachsinnigkeit hatten, sind in ihrer Entwicklung ständig nur langsam vorwärtsgesgangen, obwohl sie imstande gewesen sind, die Volksschule zu besuchen.

Ausser den obigen Fällen sind noch zwei im Alter von unter 5 Jahren zur Behandlung gekommen. Von diesen hatte der eine einen schweren Krampf gehabt, welcher sicherlich vorübergehend verschlechternd auf das Allgemeinbefinden wirkte. Das erwähnte Mädchen hat zwar mit verhältnismässig schlechtem Erfolg die Volksschule besucht, war aber danach imstande, noch die Volkshochschule und die Haushaltsschule zu absolvieren, so dass ihre Imbezillität fraglich sein dürfte. Der andere ist ein Bettnässer gewesen und ist es immer noch, aber sonst bemerken die Eltern nichts Besonderes an ihm.

Die restlichen drei Fälle waren gerade vor dem Schulalter in

Behandlung. Einer davon ist ein Taubstummer, dessen Gehör sich nach Scharlach erst vor einigen Jahren verschlechtert hat. Im Krankenhaus benimmt er sich gelindest gesagt merkwürdig, aber die fremde Umgebung, an die er sich während des kurzen Aufenthalts im Krankenhaus noch nicht gewöhnen konnte, dürfte ihrerseits das Verhalten beeinflusst haben. Später ist er in der Taubstummenschule gut weitergekommen. Es ist bekannt, dass die Tauben sehr oft einen stupiden Eindruck machen. — Der andere Fall, der die Volksschule schon angefangen hatte, war beim Eintreffen im Krankenhaus in einer gewissen Psychose, die erst allmählich verschwand. Ausserdem wurde Epilepsie diagnostiziert, obwohl später keine Krämpfe mehr vorkamen. Es dürfte auch ein gut Teil von der Quengelei des einzigen Kindes beteiligt gewesen sein, worauf auch der Umstand hinweist, dass das Mädchen zu Hause nicht ohne Beisein der Mutter seine Notdurft verrichten wollte. — Der letzte Fall hat sich wiederum von Anfang an langsam entwickelt, und war mit vieler Mühe und Plackerei imstande, 4 Klassen der Mittelschule durchzumachen, wobei er jede Klasse noch repitierte. Er ist zweifelsohne immer noch ein auf irgendeine Weise minderwertiges Individuum.

Zusammenfassend lässt sich sagen, dass bei der Stellung der Diagnose die Aufmerksamkeit auf eine mögliche andere Krankheit zu richten ist, die das Allgemeinbefinden beeinträchtigen konnte, besonders wenn es sich um unter 3-Jährige handelt. Die Krämpfe stumpfen, wie bekannt, ab. Die Taubstummheit gibt von der Person ebenfalls ein stumpfsinnigeres Bild, als es in Wirklichkeit der Fall zu sein braucht.

Bei denjenigen Fällen des Materials, die beim Eintreffen im Krankenhaus das schulpflichtige Alter schon überschritten hatten, war die Sterblichkeit, wie oben erwähnt wurde, am allerkleinsten. Von den jetzt Lebenden 23 waren 7 imstande, die Volksschule zu besuchen. Von diesen sind zwei mit der Diagnose Debilitas behandelt worden und der Rest mit der Diagnose Imbecillitas. Diese Gruppe ist zahlenmässig verhältnismässig klein, und sie ist auch viel leichter zu beurteilen als die erstere. In diesem Zusammenhang liegt jedoch kein Grund vor, näher darauf einzugehen.

Wenn wir schliesslich zusammen alle diejenigen gegenwärtig

Lebenden betrachten, welche unter dem Schulalter zur Behandlung kamen, so verteilen sie sich auf die verschiedenen Diagnosen folgendermassen: Idiotia 35, Imbecillitas 48 und Debilitas 7. Wenn wir die Entwicklungsstufe der zu einer jeden Gruppe zählenden Fälle in % berechnen, erhalten wir folgendes Resultat:

	Hat mindestens die Volksschule besucht	Spricht und geht. Unfähig für die Volksschule	Entwicklung noch schlechter
Idiotia	0 %	42,9 %	57,1 %
Imbecillitas	20,8 %	47,9 %	31,3 %
Debilitas	28,6 %	28,6 %	42,8 %

Die Einteilung in Idioten, Imbezille und Debile ist zweifelsohne auf Grund der damaligen Entwicklungsstufe vorgenommen worden. Wenn wir die obigen Zahlen betrachten, so bemerken wir, dass z. B. von den mit der Diagnose Idiotia Behandelten später kein einziger imstande war, die Volksschule zu besuchen. Dagegen gibt es solche, die weder sprechen noch gehen lernten, in allen drei Gruppen sogar verhältnismässig zahlreich als ein deutlicher Beweis für die schlechte Prognose der früh festgestellten Schwachsinnigkeit. Schon mehrere Male habe ich auf die Diagnoseschwierigkeiten besonders in den ersten Lebensjahren hingewiesen, die ausserdem durch gleichzeitig auftretende andere Krankheiten vermehrt werden. Wie oben gezeigt wurde, können sie in sehr hohem Masse sowohl auf die körperliche als auch auf die geistige Entwicklung einwirken. — Obwohl man auf Grund der durchgeführten Nachuntersuchungen keine absolut sicheren Angaben über den gegenwärtigen Zustand der behandelten Patienten erhält, und obwohl sich nicht mit Gewissheit sagen lässt, wer von ihnen sich geistig ganz normal entwickelt hat, so ist doch sicher, dass die oben erwähnte Einteilung in Idioten, Imbezille und Debile nicht dem entspricht, was wir darunter zu verstehen gewohnt sind. Die Grundlage, auf welcher die Gruppierung der Schwachsinnigen in die erwähnten Klassen durchgeführt wird, ist verhältnismässig unbestimmt und die Grenzen zwischen den verschiedenen Klassen unklar. Die Einteilung kann auf Grund

psychologischer Untersuchungen, des Intelligenz-Alters, des Intelligenz-Quotienten und der sozialen Tauglichkeit durchgeführt werden (BRABDER). Die verschiedenen Forscher ziehen die Grenzen verhältnismässig weit voneinander abweichend. In diesem Zusammenhang ist es nicht angebracht, diese Umstände näher auseinanderzusetzen. Da jedoch die verschiedenen Diagnosen eine schon endgültig erreichte Entwicklungsstufe angeben, so dürfte es begründet sein, *weil es in den ersten Lebensjahren äusserst schwierig zu sagen ist, wie sich der in Behandlung befindliche Patient entwickeln wird, auf die Differentialdiagnose zu verzichten und sich beispielsweise nur mit der Bezeichnung Imbecillitas zu begnügen, die auch als einheitliche Benennung für alle Schwachsinnigen gebraucht wird.* Dies mit umso besserem Grund, als wenigstens bei uns in den Kinderkrankenhäusern gewöhnlich relativ selten die Gelegenheit gegeben ist, ein solches Kind lange genug zu beobachten, um unbedingt richtige Schlussfolgerungen machen zu können. Um möglichst gute Ergebnisse in der Behandlung erzielen zu können, müssten wir eine Anstalt besonders für eben diese verdächtigen Fälle haben, in welche die Patienten möglichst früh zur Untersuchung aufgenommen würden, von wo aus man ihre Entwicklung verfolgen könnte, und von wo aus später jeder auf den für ihn geeigneten Weg geführt würde. Auch für die sehr schwach entwicklungsfähigen Patienten wäre die frühzeitige richtige Leitung von grösster Bedeutung.

B. Microcephalus.

Wie wir uns erinnern, verteilte sich die Sterblichkeit der Mikrocephalen ziemlich gleichmässig auf die ersten Lebensjahre. Von den Gestorbenen, insgesamt 15 oder genau die Hälfte von allen Fällen, hat sich keiner vor dem Tod nennenswert entwickelt. Kein einziger lernte sprechen oder gehen.

Unter den gegenwärtig Lebenden befinden sich indessen auch besser entwickelte Individuen, (Tabelle Nr. 11). Acht haben sowohl gehen als auch sprechen gelernt, und einer kann nur gehen. Die restlichen 6 sind vollkommen apathisch. *Keiner von ihnen war imstande, die Volksschule zu besuchen.* Vier von den besser entwickelten Fällen sind zwar noch unter 7-jährig, aber auch

Tabelle Nr. 11.

In Klammern die Anzahl der laut Mitteilung Gestorbenen.

Alter z. Zt. d. Nachfrage	Spricht nicht Geht nicht	Spricht nicht Geht	Spricht Geht nicht	Unfähig für d. Volks- schule	Hat d. Volks- schule absolviert
— 2 Jahre	0(4)	0(0)	0(0)	—	—
2—7 »	2(8)	1(0)	0(0)	4(0)	—
7—10 »	4(1)	0(0)	0(0)	1(0)	0(0)
10—20 »	0(1)	0(0)	0(0)	3(0)	0(0)
20— »	0(1)	0(0)	0(0)	0(0)	0(0)

alle diese sind so viel zurückgeblieben, dass ein erfolgreicher Schulbesuch sehr unwahrscheinlich ist. Einer von ihnen war im Alter von unter $\frac{1}{2}$ Jahr in Behandlung mit der Diagnose: Microcephalus. Idiotia (amaurotica?). Er ist jetzt 5 Jahre alt, unterscheidet sich aber laut Mitteilung mit Ausnahme der völligen Blindheit nicht von seinen Altersgenossen. — Einer von den Patienten ist ein Epileptiker und einer hat Morbus Little. — Insgesamt vier von den Mikrocephalen sind längere oder kürzere Zeit in einer Anstalt für Entwicklungsunfähige behandelt worden.

Mit Ausnahme von zwei Fällen war bei allen in Frage stehenden Mikrocephalen der Diagnose ein Vermerk über Schwachsinnigkeit beigefügt. Keiner von diesen beiden Ausnahmen lernte später gehen oder sprechen. Obwohl die Grösse des Kraniaums nicht immer in Beziehung zur Entwicklung des Intellekts zu stehen braucht, so laufen die für diese Krankheit typische Kleinheit des Kraniaums und des Gehirns fast regelmässig parallel mit der Schwachsinnigkeit. In seinem Obduktionsmaterial hat HECHTS nur zwei wirkliche Mikrocephalen gefunden (Gehirn unter 900 g), wo gleichzeitig kein geistiger Defekt bestand. In der früheren Literatur sind nach ihm ausserdem 3 derartige Fälle dargestellt worden.

Es sei noch erwähnt, dass ein früher publizierter Fall auf die Röntgenbehandlung zurückzuführen war, welche die Mutter während der Schwangerschaft bekommen hatte.

C. Idiotia mongoloidea.

Wie bekannt kann der Defekt der Intelligenz bei den mongoloïden Idioten von leichter Debilität bis zur schwersten Idiotie variieren (BROUSSEAU). In diesem Zusammenhang soll auf die Diagnostik der verschiedenen Fälle nicht näher eingegangen werden. Wir begnügen uns nur damit, kurz und in grossen Zügen auf Grund der Antworten die Schicksale der behandelten Fälle

Tabelle Nr. 12.

In Klammern die Anzahl der laut Mitteilung Gestorbenen.

Alter z. Zt. d. Nachfrage	Spricht nicht Geht nicht	Spricht nicht Geht	Spricht Geht nicht	Spricht Geht
— 2 Jahre . .	0(5)	0(0)	0(0)	—
2— 7 » . .	0(3)	0(0)	1(1)	1(1)
7—10 » . .	1(1)	2(1)	0(0)	5(4)
10—20 » . .	0(1)	2(1)	0(0)	4(1)
20— » . .	0(0)	0(0)	1(0)	0(0)

zu verfolgen, indem wir auf die schon früher erwähnte ungemein grosse Sterblichkeit hinweisen.

Aus Tabelle Nr. 12 geht hervor, dass nur sechs von den 19 Fällen, über welche nähere Angaben erhalten wurden, vor dem Tode gehen und sprechen gelernt hatten. Für die Volksschule war keiner von ihnen befähigt. — Von den am Leben Gebliebenen 17 haben 10 oder 58,8 % gehen und sprechen gelernt. Vier von diesen versuchten die Volksschule zu besuchen, mussten ihre Studien aber gleich zu Anfang aufgeben. — Einer ist jetzt 20 Jahre alt und ausserdem 6 über 10 Jahre. — Man kann mit voller Berechtigung sagen, dass sämtliche mongoloïde Idioten des Materials für den Staat nur eine Last gewesen sind.

Es sei noch erwähnt, dass keiner von den gegenwärtig Lebenden einen kongenitalen Herzfehler hat. Einer davon ist taubstumm, und ein anderer hat seit der Geburt Star.

D. Idiotia amaurotica.

Nur über acht von den lebenden amaurotischen Idioten wurde Antwort auf die Nachfrage erhalten. Von diesen waren 4 im Alter von unter 2 Jahren zur Behandlung gekommen und die restlichen vier unter dem Schulalter. Die ersteren waren alle unfähig zu sprechen und zwei davon auch zu gehen. Die letzteren wiederum sind mit einer Ausnahme unfähig sowohl zu sprechen als auch zu gehen. Alle diese haben das 10. Lebensjahr noch nicht vollendet. — Am merkwürdigsten ist der letzte Fall, der im Alter von etwas über 10 Jahren völlig apathisch und in jeder Weise gegen seine Umgebung gleichgültig zur Behandlung kam. Dieser Zustand hatte sich allmählich im Verlauf von zwei Jahren entwickelt, ohne dass vorher, soweit bekannt, eine Fieberkrankheit aufgetreten wäre. Bei der Untersuchung im Krankenhaus wurden am Augenhintergrund Veränderungen festgestellt, die jedoch nicht ganz spezifisch für die amaurotische Idiotie waren. Die Augenuntersuchung war äusserst schwierig durchzuführen. Der Patient wurde einige Tage nach der Observation ungeheilt nach Hause geschickt. Laut Mitteilung lernte er von neuem sprechen und gehen, und entwickelte sich auch sonst so viel, dass er 9-jährig die Volksschule beginnen konnte. Er ist jetzt 23 Jahre alt, hat die Volksschule durchgemacht und ist nach seiner eigenen Angabe ganz gesund. — Aller Wahrscheinlichkeit nach handelte es sich um einen langsam entwickelten encephalitischen Prozess, wobei die Differentialdiagnose sehr schwierig sein kann.

E. Hydrocephalus.

1. Hydrocephalus congenita interna: Wie wir uns erinnern, war der grösste Teil von den zu dieser Gruppe zählenden Fälle in den ersten Lebensjahren gestorben. Aus Tabelle Nr. 13 ist die endgültige Entwicklungsstufe ersichtlich. Über die als gestorben angegebenen Individuen konnten wir nur von einem geringen Teil genauere Angaben erhalten. Von den sieben Fällen, die das 7. Lebensjahr überschritten haben, lernten 3 sowohl sprechen als auch gehen, und einer hat ausserdem die Volksschule besucht. — *Von den gegenwärtig Lebenden sind 28 im Schulalter und 13 un-*

Tabelle Nr. 13.

In Klammern die Anzahl der laut Mitteilung Gestorbenen.

Alter z. Zt. d. Nachfrage	Spricht nicht Geht nicht	Spricht nicht Geht	Spricht Geht nicht	Unfähig für Volks- schule	Hat d. Volks- schule absolviert
— 7 Jahre	5(3)	0(0)	2(1)	6(1)	—
7—10 »	0(1)	0(0)	0(1)	8(1)	0(0)
10—20 »	2(0)	1(1)	1(1)	3(1)	8(1)
20— »	0(0)	0(0)	0(0)	3(0)	(0)

Tabelle Nr. 14.

Alter beim Eintreffen im Krankenhaus	Spricht Geht nicht	Spricht nicht Geht	Spricht Geht nicht	Unfähig für Volks- schule	Hat d. Volks- schule absolviert
— $\frac{1}{2}$ Jahr	4	0	1	3	0
$\frac{1}{2}$ —1 »	0	0	0	1	1
1—2 Jahre	2	0	2	6	3
2—7 »	1	1	0	8	4
7— »	0	0	0	2	2

ter dieser Altersgrenze. Zehn oder 35,7 % waren imstande die Volksschule zu besuchen, und ausserdem können 14 von den im Schulalter stehenden, was 50 % entspricht, sowohl sprechen als auch gehen. Nur 14,3 % sind schlechter entwickelt. Bei den unter 7-jährigen ist diese Prozentzahl grösser (58,3 %).

Wenn wir die in verschiedenem Alter zur Behandlung gekommenen Fälle betrachten (Tabelle Nr. 14), so lässt sich feststellen, dass sich von denjenigen, die jünger ins Krankenhaus gekommen waren, der verhältnismässig grössere Teil schlechter entwickelte. Von dem zum Sprechen und Gehen Unfähigen kamen 5 unter $\frac{1}{2}$ -jährig ins Krankenhaus und ausserdem 4 unter 2-jährig. Nur zwei waren von 2- bis 5-jährig in Behandlung. Bei den besser entwickelten Fällen ist das Verhältnis gerade umgekehrt. Von denjenigen, die unter 1 Jahr zur Behandlung kamen, hat einer

die Volksschule besucht. Bei ihm war im Krankenhaus wegen der relativen Grösse des Kopfes operative Behandlung vorgeschlagen worden, aber die Mutter war damit nicht einverstanden gewesen. Der Kopf hörte offensichtlich bald auf zu wachsen. Der Junge ist jetzt ein 16-jähriger Arbeiter, etwas langsam, kommt aber selbständig zurecht. — Von den im Alter von 1—2 Jahren behandelten Individuen waren drei fähig, die Volksschule zu absolvieren. Bei einem ist der »Balkenstich« ausgeführt worden. Vor der Operation wirkte der Patient stumpfsinnig, die Hände und die Füsse waren in verhältnismässig hohem Masse spastisch. Er begann sich allmählich zu entwickeln, lernte 4-jährig gehen, sprechen schon früher. Mit 8 Jahren fing er die Volksschule an, und ist jetzt bis auf den relativ grossen Kopf und die Schwäche der Füsse laut Mitteilung gesund. Die Operation ist in diesem Falle also offensichtlich nützlich gewesen. — Der andere Fall ist ein kongenitaler Luetiker, der antiluetische Behandlung erhalten hat. Auch er ist den erhaltenen Angaben gemäss bis auf offenbare Langsamkeit im übrigen gesund. — Der dritte Fall ist am interessantesten. Die Diagnose Hydrocephalus levis wurde bei ihm wegen der scheinbaren Grösse und der Form des Kopfes sowie der ständigen hartnäckigen Erbrechen gestellt. Das Erbrechen ging weiter bis zum Alter von 7 Jahren, wo im Zusammenhang mit akuten Bauchbeschwerden eine Operation vorgenommen wurde. Dabei stellte man fest, dass eine Darmschlinge auf irgendeine Weise in eine in der Bauchdecke befindliche Tasche geraten war, was wahrscheinlich das frühere Erbrechen hervorgerufen hatte. Der Junge ist in der 3. Klasse der Mittelschule. Er ist ein ziemlich schlechter Schüler und nässt immer noch sein Bett fast regelmässig, ist aber sonst gesund. — Alle übrigen, welche die Volksschule besucht haben, sind in späterem Alter zur Behandlung gekommen, wo der Kopf wegen der Ossifikation schwer noch wachsen kann, und die Symptome sind auch anders. Offensichtlich wurde die Entwicklung des beginnenden Hydrocephalus im Anfangsstadium unterbrochen, ohne die allgemeine Entwicklung bedeutungsvoller zu beeinträchtigen.

2. Alle diejenigen Fälle, die ausser dem Hydrocephalus noch andere Missbildungen in den Gehirnhäuten hatten, sind, wie oben

erwähnt worden ist, im Verlauf der ersten Lebensjahre gestorben, ohne dass einer von ihnen sich weiter entwickelt hätte.

3. Von den auf Entzündung der Gehirnhäute beruhenden Wasserköpfen sind 4 am Leben. Drei sind im Schulalter und zwei von diesen, beide im Alter von unter 1 Jahr an der Grundkrankheit erkrankt, waren imstande, die Volksschule zu besuchen. Der eine von diesen Letzteren hatte früher epileptiforme Krämpfe, die aber vor 3 Jahren aufhörten, und bei dem anderen musste später ein Auge entfernt werden. Im übrigen sind beide laut der Angaben vollkommen gesund. — Der Dritte ist für die Schule unfähig, kann aber doch sprechen und gehen; ist jetzt unter 10 Jahren alt. Der letzte von diesen, der im Alter von über 2 Jahren eine Gehirnhautentzündung hatte, kann jetzt noch nicht gehen.

Zusammenfassend lässt sich über alle Hydrocephalen sagen, *dass der grösste Teil von ihnen im Verlauf des ersten Lebensjahrs stirbt, aber von denjenigen, die am Leben bleiben, ist ein verhältnismässig grosser Teil imstande, sich langsam zu entwickeln, sprechen und gehen zu lernen, und ein recht beträchtlicher Teil ist fähig, die Volksschule zu besuchen.* Zu ähnlichen Resultaten ist seinerzeit MISCHE gekommen. In seinem Material waren nicht weniger als 17 % linkshändig.

Zusätzlich sei erwähnt, dass bei insgesamt 10 eine Operation vorgenommen wurde, und zwar der »Balkenstich«. Von diesen starben 8 bald nach der Operation, einer konnte später die Schule besuchen, und einer ist immer noch unfähig sich zu bewegen.

VI. Zusammenfassung.

1. Auf Grund von Nachfragen wurden die späteren Schicksale von insgesamt 469 Patienten verfolgt, die mit den Diagnosen Idiotia, Imbecillitas, Debilitas mentis, Microcephalus, Idiotia mongoloidea, Idiotia amaurotica und Hydrocephalus behandelt worden waren. Die Anzahl macht, wenn man die Hydrocephalen weglässt, 2,59 % aller behandelten Patienten aus, deren Alter von 1 Tag bis 13 Jahre variiert, und wenn man sie mitzählt, 3,79 %.

2. Bei den eigentlichen Schwachsinnigen war das Verhältnis

der Knaben zu den Mädchen ca. 4: 3 und bei den Hydrocephalen 5: 4. Bei den übrigen kamen etwas mehr Mädchen vor als Knaben.

3. Die Sterblichkeit in den ersten Lebensjahren ist in allen Gruppen gross gewesen, und sie nahm ab, je älter die Patienten zur Behandlung gekommen waren. Die gemeinsame Sterblichkeit macht bis jetzt 57,8 % aus. — Hinsichtlich der geistigen Entwicklung stand der weitaus grösste Teil beim Tode auf äusserst niedriger Stufe.

4. Die Todesursache war bei dem grössten Teil eine Infektionskrankheit. Besonders von den Mongoloiden starb der grösste Teil gerade an Lungenentzündung. — Von den Hydrocephalen starb der grösste Teil ohne eine besondere Komplikation. Zehn von ihnen wurden operiert, und davon kamen zwei mit dem Leben davon. Der eine war imstande, die Volksschule durchzumachen, aber der andere ist immer noch unfähig sich zu bewegen. Alle diejenigen, welche ausser dem Wasserkopf noch andere Missbildungen in den Gehirnhäuten hatten, starben im Verlauf der ersten Lebensjahre, ohne sich weiter zu entwickeln.

5. In je jüngerem Alter bei den gegenwärtig lebenden Fällen der geistige Defekt festgestellt wurde, umso schlechter war im allgemeinen die Entwicklung. Von den eigentlichen Schwachsinnigen war keiner von den unter 1 Jahr diagnostizierten später imstande, die Volksschule zu besuchen. Von dem im Alter von 1—7 Jahren behandelten Fällen waren 12 oder 13,3 % imstande, mindestens das Pensum der Volksschule zu absolvieren. Fünf von diesen, die alle unter 3-jährig in Behandlung waren, hatten gleichzeitig eine Infektionskrankheit. Zwei davon bekamen Krämpfe, die später verschwanden, einer hatte schwere Rachitis, einer war ein Bett-nässer und einer taubstumm. Nur drei, deren Entwicklung immer noch langsam weitergegangen ist, waren nur aus diesem Grunde in Behandlung. Die erwähnten Befunde hatten ohne Zweifel schwächenden Einfluss auf die allgemeine Entwicklung. — Von den mit der Diagnose Idiotia, Imbecillitas und Debilitas behandelten Fällen haben sich später aus jeder Gruppe solche entwickelt, die verschiedene Entwicklungsstufen erreichten. Es dürfte angebracht sein, die Differentialdiagnose wenigstens nicht sehr früh zu stellen.

Von den Mikrocephalen und den Mongoloiden war später kein einziger imstande, auch nur die Volksschule zu besuchen.

Bei den mit der Diagnose *Idiotia amaurotica* behandelten Fällen führte die Entwicklung mit einer einzigen Ausnahme mit allmählichem Verfall zum Tode. Die Ausnahme ist ein im Alter von 7 Jahren behandeltes Mädchen, das im Verlauf von zwei Jahren fähig war, die Volksschule anzufangen und jetzt nach eigener Angabe ganz gesund ist. Es dürfte sich um ein encephalitisches Krankheitsbild gehandelt haben.

Von den jetzt lebenden und das 7. Lebensjahr überschrittenen Hydrocephalen konnten 50 % die Volksschule besuchen. Nur 14,3 % sind unfähig zu sprechen und zu gehen.

Literaturverzeichnis.

- BLEYER: Amer. J. Dis. Childr. 44, 503. 1923. — — —: Ibidem 47, 342. 1934. — v. BONSDORFF: Tyksämielasten lasten hoidosta Suomessa. Suomen sosiaaliministeriön tiedonanto. 21. 1925. Helsinki. — BRANDER: Finska läkaresällsk. förhandl. 79, 409. 1936. — — —: Monatschr. f. Kinderheilk. 69, 47. 1936. — BROUSSEAU: Mongolismus. Nach Rosanoff u. Handy. — BRUSFIELD u. WYATT: Brit. j. of Childr. Dis. 23, 265. 1926. Ref. nach Zentralbl. f. Kinderheilk. 1922. — BUMKE: Handbuch der Geisteskrankheiten 1928. Berlin. J. Springer. — DOLLINGER: Zeitschr. f. Kinderheilk. 27, 332. 1921. — GODDARD: J. of nerv. a. ment. Dis. 39, 217. 1912. — HECHTS: Archiv. f. Psychiatr. 97, 64. 1932. — HELLSTÉN: Monatschr. f. Kinderheilk. 66, 400. 1936. — KOLLER: Zeitschr. jugendl. Schwachs. 8. 1912. Ref. nach Bumke. — KOLLMAN: Allgem. Zeitschr. f. Psychiatr. 40. 1884. Ref. nach Bumke. — LAHDENSUU: Acta pediatr. 21, 256. 1937. — MISCH: Monatschr. f. Psychiatr. u. Neurol. 35, 439. 1914. — PAKUNKER: Dissertation. Berlin. Ref. nach Zentralbl. f. Kinderheilk. 1913. — POTTS: Zeitschr. Kinderforsch. 31. 1923. Ref. nach Bumke. — ROSANOFF u. HANDY: Amer. J. Dis. Childr. 48, 476. 1934. — STEINEN: Monatschr. f. Kinderheilk. 35, 495. 1927. — STRECKER: Münch. med. Wochenschr. 2, 1254. 1936. — VAS: Orvosi hetilap. 65, 425. 1921. Ref. nach Zentralbl. f. Kinderheilk. 1922. — DE VRIES u. DE NEVE: Zeitschr. jugendl. Schwachs. 31. 1923. Ref. nach Bumke.

FROM ULLEVAAL HOSPITAL. EPIDEMICAL DEPT., OSLO.
CHIEF: P. M. HOLST, M. D.

Pneumothorax, Mediastinal Emphysema and Cutaneous Emphysema complicating Tracheotomy.

By
DAG RIIS.

In several different conditions there may occur pneumothorax, mediastinal emphysema and cutaneous emphysema, either separately or combined in various ways.

Pneumothorax is a relatively common condition, the occurrence of which in many disorders is a phenomenon with which most of us are familiar. Pneumothorax as a complication after tracheotomy, however, is not so well known.

Emphysema of the skin and mediastinal emphysema are both relatively rare disorders. Hereby is understood a condition in which gas or air is present respectively in the subcutaneous tissue or in the connective tissue of the mediastinum.

Apart from cases where gas is evolved owing to the presence of gasproducing microbes, cutaneous and mediastinal emphysema will practically always have a mechanical cause and be due to further extension of air through a breach of continuity in the air passages. The fundamental lesion may be localized in the trachea, bronchi or lung-tissue. The condition is often of traumatic origin and may be due to tracheotomy, injuries to the thorax with intrathoracic lesions of the air passages, complicated fractures of the ribs, thoracocentesis and, according to the literature, also bronchoscopy.

Besides these more surgical forms of cutaneous and mediastinal emphysema, the condition may arise in distinctly medical disorders which entail respiratory difficulties, especially as regards expiration. Cutaneous emphysema has been reported after

whooping cough, measles, in asthma, in diphtheria and diphtheric stenoses in the air passages and in influenza. In these cases we will almost invariably find also mediastinal emphysema and interstitial emphysema of the lungs.¹

We shall here first of all deal with the occurrence of these complications after tracheotomy.

When *cutaneous emphysema* occurs after (in) tracheotomy, we have two different possibilities to consider. 1) The emphysema may be due to the injury to the trachea which the operation entails, or 2) the existing fundamental disorder, respiratory stenosis, may be supposed to have led to pulmonary emphysema with rupture of emphysematous vesicles and consequent mediastinal and cutaneous emphysema.

A complicating *mediastinal emphysema* may arise through the last-mentioned mechanism, but it may also be imagined to have arisen in retrograde manner through transmission of air from above through the tracheotomy wound.

As regards the occurrence of *pneumothorax* there exist three theoretical possibilities: 1) Rupture of subpleural emphysematous blebs into the pleural cavity. 2) Injury to the pleural cupula during the operation. 3) Rupture of mediastinal emphysematous vesicles at the hilus into the pleural cavity.

From this it will be seen that we can distinguish between tracheotomy complications in more restricted sense, which I have called *direct tracheotomy complications*, and complications which have a deeperlying cause in the primary disorder that led to the tracheotomy operation, but in which the tracheotomy must be supposed to have played a contributory rôle. These I have designated *indirect tracheotomy complications*.

The pathogenetic possibilities which exist may be summed up as follows:

¹ The only exceptions to this rule are cases where there exist conrescences between the leaves of the pleura, so that air from an interstitial pulmonary emphysema can pass through the adhesions direct to the sub(parieto-)pleural tissue and thence to the subcutis (DOLGOPOL & STERN). Apart from this exception, a cutaneous emphysema extending from the jugulum upwards along the neck may be regarded as a certain sign of mediastinal emphysema.

A. Direct tracheotomy complications.

I. During the tracheotomy operation there may arise:

a. Independent of the respiratory phase:

Pneumothorax through injury to the dome of the pleura. (IGLAUER, who according to WIETHE was the first to mention pneumothorax as a complication in tracheotomy (1915), regards a lesion of the cupula pleurae as the cause. Further we find that WIETHE in 1933 describes two similar cases and proves by experiments that the possibility exists in case of tracheotomia inferior. A gurgling or whistling sound during the operation is regarded as a sign of injury to the pleura. MICHELS in 1939 gives such lesion as the cause in two of his six cases of pneumothorax after tracheotomy. It is a question whether also BAGER's case from 1939 does not belong here.)

b. During expiration:

Subcutaneous emphysema due to air being forced out from the trachea into the soft tissues. This may happen, for example, on accidental perforation of the trachea before it has been exposed (GÜTERBOCK). Or there may arise difficulties in introducing the cannula into the trachea, so that the aperture in the trachea comes to be covered by the deep fascia of the throat before the cannula is brought into place. (Cf. my Case No. 3.)

c. During inspiration:

Mediastinal emphysema due to suction of air down into the mediastinum through the tracheotomy wound (under certain conditions). LEINER mentions this as cause in his 9 cases of mediastinal emphysema. Cf. also GÜTERBOCK, HOFFMANN and BOYSEN.

II. After the tracheotomy operation there may arise (owing to the cannula becoming choked up or falling out):

a. During expiration:

Subcutaneous emphysema due to the air being forced out at the side of the choked-up cannula or through the tracheostoma out into the soft parts. A necessary requirement must here, moreover, be presumed to be that the lower part of the tracheotomy wound has been sutured. Moreover, the adjoining layers of tissue must not be adherent to each other in an incipient process of healing. (GÜTERBOCK's »nachträgliches Emphysem«.)

b. During inspiration:

Mediastinal emphysema due to air being sucked down into the mediastinum, where, as we know, the pressure is less than 1 atm. (from — 4 to — 6 mm Hg.). (This view is maintained by JACKSON and others. Also BOYSEN reckons with this possibility.) Both in cases I c. and II b. it is by some believed that pneumothorax may arise through rupture of mediastinal emphysematous vesicles into the pleural cavity at the hilus.

B. Indirect tracheotomy complications.

a. Mediastinal emphysema and cutaneous emphysema may be produced by rupture of vesicles in the pulmonary emphysema that has arisen on account of stenosis in the respiratory passages. Thereby is produced interstitial (interlobular) emphysema which on further transmission in the loose connective tissue along the large vessels and the bronchi, or else subpleurally, leads to mediastinal and cutaneous emphysema.

(The same mechanism must be supposed to form the basis for the occurrence of cutaneous and mediastinal emphysema in non-tracheotomized diphtheria patients, as well as in case of asthma, whooping-cough and influenza.)¹

b. Pneumothorax may arise through rupture of emphysematous vesicles on the surface of the lungs — with the possibility of valvular and perhaps, tension pneumothorax (cf. our cases).

c. Pneumothorax may also, it is claimed, arise through rupture of mediastinal emphysematous vesicles into the pleural cavity at the hilus. Likewise this form may, in the opinion of some authors, develop into a valvular and also tension pneumothorax.

¹ Cutaneous and mediastinal emphysema may occur in non-tracheotomized diphtheria patients, but rarely. OSLER says that mediastinal emphysema is occasionally seen in fatal cases of diphtheria (and pertussis). SAXL and MENDEL mention two cases of diphtheria with cutaneous emphysema in 1938. They state that similar cases had not previously been described. Analogous cases are, however, found to have been mentioned as early as in 1863 (by SCHROEDER, according to BARTELS), and some years later by SACHSE and GÜTERBOCK. It may be of interest to mention that several of these patients had been treated beforehand with emetics.

The prognosis in these cases is bad. Only one patient recovered. (One of SAXL and MENDEL's cases.)

VIRCHOW, on request, expressed his opinion respecting the pathogenesis in SACHSE's case. His conception entirely accords with the modern views, which are in part based upon the results of experiments on animals (KELMAN, MACKLIN). The post-mortem findings in SACHSE's case also confirmed VIRCHOW's conception.

Own Cases.

In the Epidemical Dept. of the Ullevaal Hospital in the years from 1940 to 1944 there were seen four cases of pneumothorax and mediastinal emphysema after tracheotomy. The first case has been reported by G. and F. BOYSEN. The diagnosis was here established on autopsy.

Since then we have seen a further three cases, all accompanied also by cutaneous emphysema. In BOYSEN's case the patient was suffering from acute laryngitis, in all the later cases from diphtheric laryngeal stenosis. In the last two cases the diagnosis was made *intra vitam*, and one of these patients recovered after treatment of the pneumothorax by repeated exsufflations.

Case No. 1.

The patient was a boy aged 2 years and 3 months, who was sent to the Epidemical Dept. of Ullevaal Hospital from the Rikshospital's Ear, Nose and Throat Dept. on ²³/₁₀ 1942.

The patient had previously had measles, had otherwise been in good health. Two days before admission he had a discharge from the right nostril. On the night before admission he had incipient respiratory difficulty, increasing in the course of the day. The doctor who was called in sent the patient to the Children's Ward in the Rikshospital under the diagnosis: »Status asthmaticus.»

On admission to the hospital the patient was almost moribund. There was severe cyanosis, violent stridor and retractions over the lower part of the thorax and in the jugulum. The auxiliary respiratory muscles were called into use. The patient was transferred to the Ear, Nose and Throat Dept., where tracheotomia superior was at once performed. Good effects from the operation.

He was then transferred to the Ullevaal Hospital's Epidemical Dept. He was bright and clear in mind, had a good colour, and seemed well. Temp.: 37.9° C. Respiration rate: 46.

Thick grayish-white, sanguinolent discharge from the nose. Red, swollen tonsils. No membrane. Lungs: normal conditions.

He was given 16 000 I. U. of diphtheria antitoxine and was placed in a steam-room.

One hour after admission he suddenly got respiratory difficulties, which rapidly increased. He became unconscious. The wound was opened and the tracheotomy opening laid bare, whereupon the cannula was again inserted. During this time it was noted that there had come a cushion-shaped swelling on the neck above the wound and on the

right cheek. The swelling gave a distinct crackling sound like that of a snowball.

The child still remained unconscious. After 1 ml. of coramin intravenously he got transient convulsions. He died shortly afterwards.

On autopsy there was found: Coherent membranes in the larynx and 2-3 cm. downwards in the trachea. Sanguinolent fluid from the aperture in the trachea down into the bronchi. In the mediastinum ant. was seen a pronounced mediastinal emphysema with vesicles up to the size of a nut. Further there was found pneumothorax on both sides, and on the left side tension pneumothorax. Both lungs were atelectatic. Microscopy of sections from the lungs showed extreme hyperemia and there was so little aeration that the ordinary structure of the lung could not be distinguished.

Case No. 2.

Herman V. K. The patient was a boy aged 1 year and 9 months, who was admitted to the Epidemical Dept. on 13/6 1943 under the diagnosis «Croup». Discharged on 2/7 1943.

He had eczema when a nursing and had been much troubled by a cough in the first year of life. Had twice had «slight pneumonia». Otherwise healthy.

Four days before admission he got fits of coughing, sometimes followed by vomiting. On the night before admission incipient respiratory difficulties. Temp. 39° C.

On admission to the hospital in the afternoon of 13/6 the patient was found to be a boy aged 21 months, big and strong for his age. He was in cold perspiration, very pale, with cyanotic lips, fingers and toes. The respiration was very laboured, audible and stridorous. Great retractions in the jugulum, in the fossae supraclaviculares and over the lower part of the thorax. The throat was difficult to inspect, both on account of abundant mucus and because the patient was very unquiet. There seemed to be a yellowish coating on the posterior wall of the pharynx.

Immediately after his admission *Tracheotomia inferior* was performed in ether narcosis. The operation proceeded in regular manner, except that the incision in the trachea came a little to the right of the median line, owing to the operation having to be done in great haste. Cannula No. 2 was inserted. Good effects from the operation. He was given 16 000 I. U. of diphtheria antitoxin, and was placed in a steam-room.

The patient continued to be very unruly, was difficult to manage and made violent resistant movements. The respiration gradually became laboured again. Twelve hours after the operation the doctor on duty was summoned. The cannula had evidently slipped out, and a

re-examination of the wound was at once made. After some effort cannula No. 3 was inserted.

The condition then improved for some hours, but in the course of the forenoon the patient again became greatly distressed. The cannula now lay in the right place, there was undoubtedly clear passage of air and a feather could be pushed far down without resistance. The boy was still very unquiet. He was cyanotic, appeared to be greatly distressed and exhausted. There was little retractions in proportion to the great difficulty in breathing. There was considerable emphysema on the neck and over the anterior surface of the thorax. Short, but distinct respiratory sounds over the anterior surface of the lungs. There were numerous abnormal sounds, but these were obviously due to the subcutaneous emphysema that had spread down over the thorax. The percussion sound was also difficult to judge owing to the emphysema of the skin. But there was some difference in the percussion sound on the posterior surfaces, the tone being more «hyperresonant» on the right side. The respiratory sound was also somewhat fainter here.

Neither was the position of the cannula quite ideal, for the passage of air became somewhat better when the cannula-shield was pushed a little upwards and to the right.

Pneumothorax was suspected, but the patient's condition was such that there could be no question of employing the most obvious diagnostic aid — radiographic examination.

As the condition did not improve, a puncture was made at midday with a thin needle on the right posterior surface, without any escape of air being noted. Some time later a new thoracocentesis was made with an ordinary pleural puncture needle and the pressure was measured and found to be about 30 cm. H_2O .

On exsufflation of about 250 ml. of air the pressure became negative (-2 to -3 cm.). The right half of the thorax showed distinctly better movement after this, and the respiratory sound was noticeably stronger.

The patient was now better for some hours, but at 11 p. m. he became so greatly distressed that exsufflation was again employed. The pressure was now 35 cm. H_2O . After 300 ml. had been tapped the pressure again became negative. Immediately after this operation the patient was worse rather than better, but his condition improved somewhat when he came to rest.

Altogether the patient was quite exceptionally unruly and violent. His display of strength was often simply incredible, considering what his condition was otherwise. His unruliness complicated in high degree the work both of the nurse and the doctor.

On the following night he got some sleep. In the morning of the 15/6 he got a fresh attack of dyspnoea. The respiration was superficial.

The emphysema of the skin had spread still farther. Negative pressure was now measured on both sides.

During the forenoon his state was perhaps somewhat better, but the respiration was still laboured and he got no rest. In the afternoon there was still no sign of reproduction of the tension pneumothorax and he seemed a little better.

Already on the next day the cannula could be removed.

On $17/6$ he could be sent for radiographic examination, which revealed a pneumothorax on the right side, with partial atelectasis of the lung. Subcutaneous emphysema.

Radiographic control examination on $23/6$ still showed dextral pneumothorax, whereas a renewed examination on $2/7$ no longer showed signs of air in the pleural cavity.

The cutaneous emphysema disappeared after 5 or 6 days.

The further course of the illness was uncomplicated, apart from a transient serum exanthema.

In samples taken both from nose and throat on the day of admission Diphtheria bacilli were found.

Case No. 3.

Rolf L. The patient, a previously healthy 6 year-old boy, was admitted to the Epidemical Dept. on $3/7$ 1943.

The day before admission he became hoarse and complained of difficulty in breathing. Slight bleeding from the nose.

On admission he was cyanotic. Whistling respiration, now and then «laryngitic» cough. Voice bad, but not quite aphonic. Respiration laboured, with use of auxiliary respiratory muscles. Temp. 37.5°C .

Nose: Reduced passage of air. Incrustation in nostrils. Gray-yellow pellicle on the tonsils and posterior wall of the pharynx.

Lungs: sibili over the anterior and posterior surfaces.

Immediately after admission the patient was given 24 000 I. U. of diphtheria antitoxin and was placed in a steam-room.

Next day he received a further 12 000 I. U. of diphtheria serum.

Four hours after admission his condition had become worse. The cyanosis had increased. Respiration 28, audible. Great retractions. Aphonic.

Tracheotomia media was now performed. There was some difficulty in inserting the cannula into the trachea. While this was being done there came considerable emphysema on the neck. In the trachea there was seen sanguinolent secretion, but no membranes.

Temp. rose next evening to 38.8°C ., wherefore he was given sulfathiazol.

On the day after admission it is recorded that there had been good passage through the cannula the whole time, except that it occasionally

became choked up by membranes. Now and then he coughed up fragments of membrane, and some could also be aspirated. The cough was weak. The respiration had the whole time since the operation been laboured and superficial. The cyanosis varied somewhat in intensity, but did not entirely disappear. He had considerable emphysema, extending over the whole of the anterior surface of the thorax and on the right side of the face up to the right eyelid. Over the right lung were heard numerous subcrepitant râles. The respiratory sound was weakened on the anterior surface. On the right side was tympanic resonance on percussion, while the respiratory sound was hardly perceptible.

The pressure in the pleural cavity on the right side was found to be 28 cm. H_2O . After exsufflation of about 250 ml. of air the pressure became negative. The respiration became somewhat easier, but was still laboured and one got the impression that the lungs were stuffy far down in the chest.

He became steadily worse and died in the morning of $5/7$, two days after admission.

Diphtheria bacilli were found in cultures from the secretion in the throat and nose.

The post mortem diagnosis was: «Laryngotracheobronchitis diphtherica. Bronchopneumonia. Emphysema colli, thoracis et mediastini.» The examination revealed numerous pseudomembranes on the posterior surface of the epiglottis and in the larynx. Also down in the large and small bronchi many membranes were found, especially on the left side, where there was also some pus. The right lung was somewhat atelectatic. The left lung was infiltrated, with numerous pneumonic foci. Some emphysematous vesicles in the upper part of the mediastinum.

It will be noted that nothing is said as to pneumothorax, which must have been overlooked.

Both of the two last cases differ from all previously reported cases by the fact that the diagnosis was not made after X-ray examination, but by *direct measurement of the pressure in the pleural cavity*, after the clinical findings had aroused suspicion of pneumothorax.

When once we have become aware of the fact that pneumothorax may occur as a complication after tracheotomy, we can hardly avoid thinking of this condition in a situation where the possibility thereof exists. The difficulty lies in the verification of the diagnosis. And here it is natural to have recourse to radiographic examination. In our cases such examination was quite out of the question, as the patients were too ill to be moved, and

neither could the Department's own transportable apparatus be employed. But the last two cases show that we can reach the goal without the help of radiography.

It must also be emphasized that without prior knowledge of the condition the diagnosis will always be difficult, unless, indeed, it is revealed by a more fortuitous radiographic examination.

Frequency of the Complications.

In the period from $\frac{1}{1}$ 1940 to $\frac{1}{7}$ 1944 79 tracheotomies were performed in the Epidemical Dept. of the Ullevaal Hospital. In the same period there were seen, as above stated, four cases of pneumothorax and mediastinal emphysema. It is, of course, impossible on the basis of these findings to draw any conclusions as to the frequency of the complications. But, on the other hand, they invite to certain reflections. To judge from the available literature, the complications are very rare, especially as regards the occurrence of *pneumothorax*. The lack of interest shown for the condition in the ordinary textbooks and manuals points in the same direction. To take some examples, we find no mention of the complication in »Nordisk Lærebok i Intern Medisin eller Kirurgi». Neither is it mentioned in »Neue Deutsche Klinik», »Abts Textbook of Pediatrics», or in the German textbook of pediatrics by PFAUNDLER-SCHLOSSMANN. Even CHEV. JACKSON and CHEV. J. JACKSON devote only a few lines to the condition in their book »The Larynx and its Diseases».

In HOCHENEGG and PAYR's textbook of surgery, published in 1932, it is mentioned that *cutaneous emphysema* is a very common complication and also that *pneumothorax* may occur.

In Scandinavia there have earlier been described only three cases of pneumothorax after tracheotomy, none of which occurred in connection with diphtheria (SELDÉN, BAGER, BOYSEN).¹

¹ In 1903 in his work on the causes of death in diphtheria E. FABER mentions a case of cutaneous and mediastinal emphysema. He believes that the mediastinal emphysema was the cause of death. The case has so many points of resemblance to our cases that I am personally inclined to think that pneumothorax existed also in FABER's case. This is also more likely to have

The apparent accumulation of cases in our hospital in the period mentioned may, of course, be merely fortuitous. Or it might be supposed to be due to special circumstances connected with the method of operation. Meanwhile, it must be noted that in each of the four cases the operation was performed by a different surgeon and in three different forms, namely, tracheotomy sup. (twice), tracheotomy media and tracheotomy inferior.

Whereas isolated cutaneous emphysema must be regarded as a wellknown occurrence after tracheotomy, we had not in our department been alive to the possibility of mediastinal emphysema and pneumothorax as complications prior to the occurrence of the first-mentioned case (BOYSEN'S). It may obviously be assumed that the condition is more frequently present than would appear from the literature, but that it is often overlooked. Even in case of autopsy a pneumothorax may easily escape notice if attention is not especially directed to this condition. (Our Case No. 3, where a clinical pneumothorax was undoubtedly present, illustrates this fact, seeing that pneumothorax is not mentioned in the report of the autopsy.)

We also find it stated by most authors that the condition is certainly more frequent than appears from the reports in the literature.

I have sought to find an expression for the frequency of the complications, judging from older statistics embracing tracheotomies in children with croup. I have further included information given in reports of case-histories where the author has mentioned the number of tracheotomies performed within the period in which the cases occurred. The results will be found in *Table I*.

As will be seen, the figures vary greatly. When HABS and WANSHER in their investigation of respectively 572 and 400 cases do not mention these complications it is natural to suppose that they have escaped attention.

been the immediate cause of death than the relatively benign mediastinal emphysema. (I here disregard traumatic med. emphysema.)

The account of the autopsy in FABER'S case unfortunately gives no definite evidence in support of my assumption.

Table I.

Author	Year	No. of patient	Died	Cut. emphys.	Cutaneous emph. + med. emph.	Med. emph. alone	Cutaneous emph. + med. emph. + pneumothorax	Pneumo-thorax alone	Pulm. emph. and interstitial emphysema
BARTELS (partly cit. GÜTERBOCK)	1867	57	44	5		3			
Dr. HASSE	1868	26	15						
P. GÜTERBOCK	1871	167	?	10	3				
WANSCHER (cit. SCHÜLLER)	1868—1876	400	230						
V. HUGONNAI	1868—1877	101	73	6					
ROBERT JERRY	1892	214	119	1					3
RUDOLPH HABS	1892	572	316						
Other works, where the number of tracheotomies in a certain period is stated in connection with case reports:									
CARL LEINER	1903	12	4		8	1			
CAMILLO WIETHE	1923—1933	50	?					2	
GRAEBNER	1939	20			1	3			
Ullevaal. Dept. I	1940—1/1 44	79	21				3+1 ¹		
Total		1 698		22	12	7	3+1 ¹	2	3

¹ Only med. emphysema + pneumothorax.

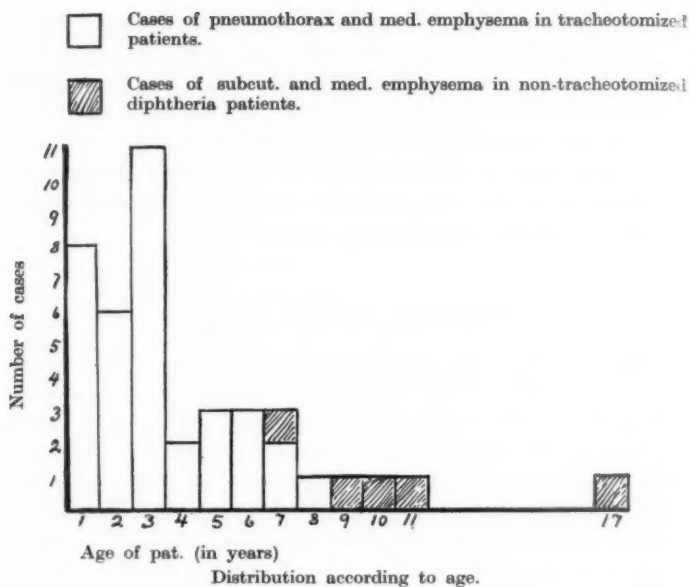
On the other hand, it seems improbable that LEINER's report of 9 cases of mediastinal emphysema among 12 tracheotomized patients gives even an approximately correct picture. Special circumstances must here be supposed to have come into play, such as, for example, special operative technique. For all LEINER's cases were in his opinion to be regarded as tracheotomy complications in the more restricted sense, *i.e.*, as being occasioned by local conditions attending the operation itself.

Distribution According to Age.

MICHELS, who also believes that the complication must be of more frequent occurrence than hitherto supposed, finds his view partly on the results reported by FIGI, who in his statistical account of 200 tracheotomies does not mention the condition. Meanwhile, FIGI's material is derived from an otolaryngological and an ordinary surgical hospital and embraces adult patients with non-acute stenotic processes, including 133 cases of cancer. Only 43 % are emergency operations. It could therefore beforehand be expected that he would not find cases of pneumothorax and mediastinal emphysema in that material, since all earlier reports respecting these complications in the literature concern children.

In order to give an idea of the distribution according to age I have set up a diagram which embraces the cases of pneumothorax and mediastinal emphysema that I have been able to find in the accessible literature (in the summer 1944). I have also entered separately the cases of cutaneous and mediastinal emphysema I have found reported in non-tracheotomized diphtheria patients.

It is seen from this diagram that among 36 cases of these complications, arising after tracheotomy, there is found no patient over 8 years old. In 27 of the 36 cases the patients were under 4 years of age. Thus the complications belong in marked degree to the years of childhood.



Earlier Reported Cases of Pneumothorax after Tracheotomy.

For judging about prognosis of the condition and the possibilities a particular situation may present it is of considerable interest to arrive at a clear understanding of the pathogenesis in the individual cases. As regards the mechanism of production, there exist, as before mentioned, many possibilities, and the different authors do not always give the same explanation in apparently quite analogous cases.

In Table II I have given a survey of the hitherto reported cases of pneumothorax complicating tracheotomy which I have under the existing circumstances had an opportunity of assembling.

The table gives some idea of the prognosis regarded in relation to the presumed mechanism of production.

As will be seen from the table, I have altogether 13 cases, reported by 8 authors, including 1 case occurring in diphtheria.

The distribution of the cases will be seen from Table III.

Mechanism of Production.

A fundamental requirement in the discussion of the pathogenesis must be that the theories and assertions advanced do not conflict with the laws governing the special mechanico-physical conditions prevailing for the lungs and their relations to the thoracic wall — conditions to which one inevitably must constantly revert when it is a question of adopting a standpoint towards the different theories.

Various experiments have been carried out both on living animals and on human corpses in order to make clear the pathogenesis. But here, as elsewhere in medical research, one must be cautious in applying conclusions drawn from experiments on animals to the conditions in human beings. In the first place it is difficult to attain such experimental conditions that one can entirely imitate the pathological processes that take place in man. And, besides, one cannot count upon the anatomical-physiological conditions being identical. A pointer in this direction is furnished by the great difference noted in the occurrence of the complications in the different age-groups in man.

As an example of an experiment, which, it is true, lies a little outside our subject, may be mentioned JOSEF KEIS's attempt to arrive at an understanding of the mechanism of the production of pneumothorax in operations for suprasternal struma. He blew air down into the mediastinum by means of a cannula through the sternum or in the jugulum in corpses and found that in this manner there could be produced cutaneous and mediastinal emphysema and pneumothorax. Quite apart from the question whether his observation is correct, we cannot well imagine such a situation to arise during tracheotomy or other operations on the neck as that air would be forced down under positive pressure into the mediastinum. Air from outside could come into the mediastinum only by suction.

Table II.

Author	Year	Patient's age	Primary disease	Complication	Author's conception of pathogenesis	Treatment	Final result
WIETHE »	1933 6 years 1933 5 »		Oedema subglottidis Laryngeal papiloma	Pneumothorax »	Lesion of pleural dome during the operation in both cases	None	Cured »
NEFFSON, BULLOWA	1938 2 »		Influenza. Laryngo-tracheobronchitis	Bil. pneumothorax, med. and cut. emph.	Pleura injured during op., but author supposes pn.-th. existed beforehand. (Pleura, unaccompanied by lung protruded into oper. wound.)	Exsufflation	Died
WISSLER	1939 3 »		Cong. anomaly of trachea with compression from struma	Cut. emph., med. pn.-th. and dextral emph. Pneumonia? (Atelectasis? — Present author's remark.)	Author adopts no definite standpoint	Exsufflation	Cured
MICHELS	1939 3 » Case 1		Stenosis in right main bronchus	Cut. & med. emph. Later moderate pn.-th.	No particular remarks	None	»
	3 mths Case 2		Cong. laryngeal stenosis	Med. emph. and limited pneumothorax	» » » »	None	Died
	2 years Case 3		Morbili-group	Cut. emph., med. emph. and bil. pn.-thorax	» » » »	Indefinite quantity of air aspirated	»
	1 year Case 6		Ac. laryngotracheobronchitis	Bil. valvular pn.-th. + med. emphysema	Thinks the cause was probably lesion of pleura during operation. This can hardly explain subse-	Repeated aspiration on both sides	Died

1 Year Case 5	Ac. laryngotracheo- bronchitis	Bil. valvular pn.th. + med.emphysema	Thinks the cause was prob- ably lesion of pleura dur- ing operation. This can hardly explain subse- quent bil. pn.th.	Repeated as- piration on both sides	Died
18 mths Case 6	Bean in right main bronchus	2 days after tracheo- tomy dextral pn- th. (pat. was bron- choscope)	No particular remarks. (The bronchoscopy?—Present author's remark.)	Permanent drainage	Cured
1939 8 years SELDEN	Laryngeal papilloma	Dextral pn.thorax + med. and cut. emph.	Pn.thorax due to rupture of subpleural blebs. Med. emph. and cut. emph. due to transmission of inter- stitial emph. along the bronchial tree to the hilus	Permanent drainage	Died
1940 2 1/2 years DOLGOPOL, STEEN	Diphther. laryngitis and bronchitis in earlier tracheoto- mized pat. who had had emphyema	Sinistral pn.thorax and cut. emphy- sema	Diffusion of air via inter- stitial emph., partly along lymphatic ducts through adhesions into pleural cavity and sub-(parieto-) pleural tissue to the sub- cutis	Aspiration	»
1942 5 years BAGER	Laryngeal papilloma	Dextral pneumotho- rax	Rupture of alveoles owing to pulm. emph. due to chron. laryngeal stenosis, combined with the acute attack of suffocation	None	Cured
1942 9 mths BOYSEN & BOYSEN	Acute laryngitis (Pseudocroup)	Bil. pn.thorax + med. emphysema. Dia- gnosed post mor- tem	Med. emphysema through transmission of inter- stitial emphysema. Pn- thorax due to rupture of subpleural emph. ve- sicles	None	Died

Table III.

	Cured	Died
4 pat. had isolated pneumothorax	4	0
3 » » pneumothorax with med. emphysema, including two cases of bilateral pn.th.	0	3
1 » » pneumothorax+cutaneous emphysema	0	1
5 » » pneumothorax+med. emphysema and cnt. emphysema. 2 of these had bilateral pneumothorax. Of the two who recovered one had moderate pneumothorax. The other recovered after adequate treatment. (WISSLER's case.)	2	3

Discussion of the Different Pathogenetic Possibilities.

Cf. the survey on pp. 323—324.

As regards *Point A I a*, — occurrence of pneumothorax through direct lesion of the cupula pleurae — WIETHE has shown that this possibility exists in case of tracheotomia inferior. The dome of pleura may, on account of respiratory difficulties due to tracheal stenosis, rise above the jugulum, and this movement is favoured by the position of the patient during the operation.

Under these circumstances it must be presumed that the lung will be drawn up together with the pleural dome and that there is also some risk of injury to the lung-tissue itself. But even if the lung should be damaged, it is not probable that there would thus be created a valve mechanism which might lead to valvular pneumothorax. This is a matter of some significance for the judgment of the prognosis. As already mentioned, all the patients with this form of pneumothorax recovered. None of them needed exsufflation. In cases *without* injury to the pulmonary tissue the possibility of valvular pneumothorax arising through this mechanism may, we must suppose, be left out of consideration, even though, theoretically, it can hardly be entirely excluded.

MICHELS entirely agrees with WIETHE's conception of this mechanism of production. Meanwhile, he makes a remark which upsets the foundation for his judgment of two of his own cases. MICHELS says: 'The observation has been made on several occasions that pleura *unaccompanied by lung* has protruded into the

tracheotomy wound.* This cannot be imagined to have occurred without a pneumothorax being present beforehand. NEFFSON and BULLOWA adduce precisely this phenomenon as basis for their assertion that in their case a pneumothorax existed already before the operation.

From a purely theoretical standpoint it should be self-evident that the pleura cannot rise above its usual position without being accompanied by the lung, on account of the vacuum existing in the pleural cavity. The case will be different if air has entered into the cavity beforehand.

In MICHELS's Cases 4 and 5 there was during the operation observed a protrusion of the pleura into the tracheotomy wound. Here there may either have existed a pneumothorax beforehand, which is probable in Case 5, or else the pleura has been accompanied by the lung, which has probably been the case with Patient No. 4. This should then be analogous to WIETHE's cases — presuming that a pneumothorax really occurred, due to the supposed lesion of the pleura during the operation. There was heard during the operation a whistling sound, which was taken to indicate that the pleura had probably been damaged. A radiograph taken on the following day gave no evidence of the presence of a pneumothorax, to judge from the description given of the picture. I have therefore not included this case in my synoptic table (Table II).

In Case 5 there was afterwards noted a bilateral valvular pneumothorax, a fact which further confirms the assumption that here there did not exist a direct tracheotomy complication, as MICHELS seems to think, but that pneumothorax was present already prior to the operation.

BAGER's case can also be best explained by assuming a direct lesion of the pleura during the operation, or a perforation of the pleural cupula (and possibly of the lung tissue) during anesthetization. This latter supposition accords with the fact that the patient's respiratory difficulties increased enormously after administration of the local anesthetic. To judge from the subsequent course it is reasonable to suppose that a simple pneumothorax existed, and both the course of the case and the absence

of cutaneous and mediastinal emphysema speak for the theory of injury to the pleura during the operation, or possibly perforation of the pleura and lung during anesthetization.

Point A I b.

It is immediately obvious that subcutaneous emphysema must arise during expiration since the skin is the whole time subjected to the atmospheric pressure, which must be overcome by the air that is forced out into the tissues. Emphysema arising in this manner is usually not particularly wide-spread and is a more troublesome than dangerous symptom. As soon as the cannula is in its place the danger of further extension is over, a point on which agreement seems to prevail among the different authors.

Point A I c.

This mechanism for the production of mediastinal emphysema is emphasized by several authors (GÜTERBOCK, LEINER, BOYSEN). In this connection GÜTERBOCK quotes the description of an operation given by HOFFMANN, which in my opinion is illustrative of what takes place in this situation. In his description of an operation performed on account of the presence of a foreign body in the trachea HOFFMANN says:

«The thyroid gland was held up by means of an eyelid-hook after the veins on its lower border had been ligated. During some violent respiratory movements which occurred every time it was attempted to introduce an artery-forceps there came a peculiar sound, such as I had once before noted during a tracheotomy. I thought at first that the trachea had been injured by the point of the scalpel — an assumption which, however, was unfounded, as I had in the deeper layers of tissue used only the shaft of the scalpel and an anatomical pincette. On further investigation I finally found the cause of the phenomenon. On deep inspiration the loose tissues in the upper aperture of the thorax are drawn back a little from the sternum and, as the edges of the wound were all the time held apart by blunt hooks, there was formed a cavity, to which the air gained admission through the wound. When an expiration now followed, all the soft parts in the anterior region of the neck rapidly become displaced, the supply of air to the cavity thus formed is restricted or cut off and some of the air in the cavity is forced out into the tissues, while some escapes in bubbles with a whistling sound through the blood which in the meantime has collected at the bottom of the wound.»

GÜTERBOCK, who had several times had the same experience as HOFFMANN, believes that in each case it is a question of a thymus that projects high up. He says: »During the violent respiratory movements the deeper parts of the wound are displaced and the air can gain access between the thymus and the thyroid gland. By holding a small sponge against the wound the absorption of air is at once reduced.« This is an experience which we, too, have repeatedly had.

BOYSEN's conception of this mechanism, namely, that air is sucked into the mediastinum during inspiration and by means of a valve-mechanism is retained during expiration, so that the pressure gradually increases and finally becomes positive, is theoretically unthinkable, if it is meant that the pressure is positive in both respiratory phases. During inspiration the pressure cannot under any circumstances become greater than that of the external air, with which the mediastinum is in communication in each inspiration.

Moreover, the condition must be deemed to be more suitable for a valve-mechanism working in the opposite direction, at any rate when the edges of the tracheotomy wound are no longer held apart by hooks. The most reasonable supposition is that an essential part of the air bubbles out again during expiration (cf. HOFFMANN).

Since we know that air in the mediastinum is normally found to escape through the subcutaneous tissue of the throat as by a natural safety-valve, even where tracheotomy has not been performed, there seems to me to be little reason for supposing that mediastinal emphysema arising in this manner will become so extensive as to represent any serious complication.

It is stated that mediastinal emphysema arising in this way may possibly lead to pneumothorax, but no cases supporting this view have been reported. The previously mentioned cadaver-experiment made by JOSEF KEIS is not convincing. At all events, it seems reasonable to suppose that there must be less resistance to the escape of an emphysema to the connective tissue of the throat, at any rate in case of tracheotomized patients. GÜTERBOCK also regards this complication as not being very dangerous.

Point A II a and b.

When the cannula after the operation either glides out or is choked up, for example, by fragments of membrane, and at the same time there is room for air to pass along the outside of the cannula, air may be forced out from the trachea during expiration. If the wound is sutured, the air cannot escape outwards, but is forced in under the soft tissues. So far as I can understand, this must be the chief reason why we should refrain from suturing the tracheotomy wound below the cannula, but should merely employ tamponage, as is strongly emphasized by JACKSON, among others. When other authors (BOYSEN) believe that we should refrain from suturing and adopt tamponing instead in order to prevent the occurrence of mediastinal emphysema owing to absorption of air through the tracheotomy wound into the mediastinum, it is difficult to understand why this could not be attained equally well by suture as by tamponage. When also JACKSON speaks of mediastinal emphysema in this connection, I understand him to mean that the danger that mediastinal emphysema may arise *indirectly* through transmission of a subcutaneous emphysema is eliminated by omitting the suturing.

CHEV. JACKSON and CHEV. J. JACKSON says: »Subcutaneous emphysema may arise, and this is of no consequence unless the error of stitching up the wound has been committed. If so, all the stitches should be removed, otherwise mediastinal emphysema may develop from working of the air along the tissue layers under the deep fascia, aided by the normal negative pressure at each inspiration. It may even reach the pleural cavity, causing pneumothorax.»

A transmission of the cutaneous emphysema to the mediastinum could take place only during inspiration, as also JACKSON remarks, since it must be assumed that the increased pressure in the thorax on expiration would prevent any entrance of air into the mediastinum in this phase of respiration. It must be presumed that a subcutaneous emphysema arising and increasing during expiration could continue to spread in all directions in the subcutis independently of the respiratory phase so

long as the air is under a pressure of more than 1 atm. Under these circumstances it is reasonable to suppose that the diffusion in the subcutis, which can proceed continuously, would meet with less resistance than an extension also to the mediastinum, which would be counteracted by the increased pressure in the mediastinum during each expiration. It is also difficult to believe that the negative pressure in the mediastinum which JACKSON mentions could afford any help in the transmission of air through the minute interstices of the tissue, which would offer considerable resistance to any suctional action.

It is likewise improbable that a pneumothorax might be brought about through a further development of this mechanism. And neither JACKSON nor other authors who maintain this view as to one of the possible mechanism for production of mediastinal emphysema and pneumothorax refer to any cases in support of their assumption.

Point B a.

On this point there has evidently prevailed full agreement as to the mechanism since VIRCHOW's days. It is the same mechanism as that which operates in the production of cutaneous and mediastinal emphysema in case of stenotic processes in the air passages where tracheotomy has not been performed, for instance, in case of diphtheric stenosis or foreign bodies in the trachea, and further in whooping cough, asthma, influenza etc.

Point B b.

Parallel with the production of mediastinal emphysema through the above-mentioned mechanism we may get pneumothorax through rupture of a subpleural emphysematous bleb. KIRSCHNER states that a pressure of 200 to 300 mm. of water is required to cause a subpleural vesicle to burst — a pressure which may easily arise under these circumstances (cf. STARLING, FENICHEL). A pneumothorax produced in this manner may be a valvular and, possibly, a tension pneumothorax.

Point B c.

Pneumothorax due to rupture of mediastinal emphysematous vesicles into the pleural cavity at the hilus. This view is based partly on experiments on animals (MACKLIN, cited by MICHELS). Many authors find this mechanism very probable, a view with which I cannot agree. That it can also give occasion to tension pneumothorax, as some believe, I find, however, quite improbable. In that event, the air would have to take the following course: From bronchi *via* alveoles through the lung tissue, as interstitial emphysema, to the connective tissue of the mediastinum and therefrom to the pleural cavity. The pressure in the mediastinum would have to stand all the time on a level with or higher than the pressure in the pleural cavity in order to enable the air to be forced from the mediastinum into the pleural cavity and produce overpressure there. The air in the mediastinum will much more easily be able to escape *via* the cervical connective tissue, where the resistance to be overcome is the resistance of the tissues only.

As regards the mechanism in our cases, it is probable that the *cutaneous emphysema*, at any rate in the last two cases, has primarily been a direct tracheotomy complication, arising in Case 2 through the cannula having fallen out and in Case 3 through the air having been forced out into the tissues through the aperture in the trachea before the cannula was in its place. In all cases the respiratory difficulties increased, after an interval in which the condition had been satisfactory. During these renewed exertions there developed a *mediastinal emphysema* and further *cutaneous emphysema*, as the cutaneous emphysema also in Cases 2 and 3 increased considerably even after the cannula had come into its place in the trachea. In all three cases the *pneumothorax* is presumed to have been occasioned by rupture of an emphysematous bulla on the surface of the lung. For in each of the 3 cases there was found tension-pneumothorax.

One may ask oneself what is the reason for the more frequent occurrence of this complication in tracheotomized patients than in those with corresponding diseases where tracheotomy has not

been performed. *One* explanation may be that the great majority of patients with a serious stenosis of the air passages are operated so early that the complication has not time to develop beforehand.

Another, and possibly essential, consideration is the following: A diphtheria patient with considerable stenosis — usually the patients are very young children — will relatively soon become so greatly affected and weakened through anoxemia that the respiratory efforts will by degrees become fainter. The retractions may under these circumstances be only little pronounced and the whole picture of a patient with laryngeal stenosis may become indistinct, so that the diagnosis may even be rendered difficult. (A fact which is emphasized by HABS a. o.) After the tracheotomy the child quickly rallies, comes to rest and gets a refreshing sleep. When, owing to choking up of the cannula or because it has fallen out, symptoms of stenosis suddenly arise again, the child can with renewed vigour take up the struggle to overcome the obstruction. It must be assumed that already beforehand pulmonary emphysema and interstitial emphysema have existed. And owing to the great and sudden changes of pressure which the violent renewed efforts entail the emphysema rapidly continues to develop, possibly with resultant pneumothorax.

Summary.

After a brief account of the disorders in which pneumothorax and mediastinal and cutaneous emphysema may occur the author gives a survey of the theoretically possible mechanisms which may operate in the production of these conditions after tracheotomy. He divides the complications into two groups: *Direct tracheotomy complications*, due to the operation itself, and *indirect tracheotomy complications*, the ultimate cause of which must be sought for in the existing primary disease, but in which the tracheotomy must be assumed to play a contributory rôle.

Three cases observed by the author himself are described, in each of which a patient with diphtheria got tension-pneumothorax, mediastinal emphysema and cutaneous emphysema in

the course of the first hours following the operation, after an interval of relatively good condition.

While the diagnosis in the first case was established only on post-mortem examination, in the two last cases the condition was diagnosed *intra vitam* by direct measurement of the pressure in the pleural cavity, as radiographic examination could not be carried out. The two last patients were treated by exsufflation, and one of them recovered. The other had diffused diphtheric changes right down in the finer branches of the bronchi.

The author discusses the frequency of the complications and, in common with other authors, he is inclined to think that the condition is of more frequent occurrence than would seem to be suggested by the reports to be found in the literature.

As regards the age distribution it is pointed out that the complications seem in marked degree to belong to the years of childhood, seeing that there have not been reported any cases of mediastinal emphysema and pneumothorax after tracheotomy in patients over 8 years old. Of 36 patients 27 were under the age of 4 years.

The prognosis in cases of pneumothorax seems to depend upon the mechanism of production, since all patients with pneumothorax due to direct injury to the pleura during the operation are seen to have recovered, whereas the prognosis in pneumothorax occurring as a so-called indirect tracheotomy complication is very unfavourable, at any rate in the absence of treatment.

In conclusion the different pathogenetic possibilities are discussed.

The author believes that the direct tracheotomy complications may generally speaking, be regarded as less dangerous. The only possibility for the occurrence of pneumothorax in this group is deemed to lie in a direct injury to the pleura during the operation.

In the indirect tracheotomy complications the cutaneous emphysema is merely to be regarded as an incidental phenomenon in an existing mediastinal and interstitial emphysema. Here the conditions are favourable for the development of pneu-

mothorax, a valvular and, perhaps, tension-pneumothorax, which may rapidly lead to death.

Repeated exsufflations is presumed to be the only method of treatment which is practically feasible in case of these unruly little patients, where continuous drainage presents great difficulties.

In the cases here described there seems to have existed a combination of both mechanisms: cutaneous emphysema occasioned by the forcing out of air from the tracheotomy-opening when the cannula had fallen out or become choked up, and afterwards mediastinal emphysema arising through further transmission of an interstitial emphysema, and pneumothorax due to rupture of subpleural emphysematous vesicles.

In conclusion the author seeks to give an explanation of the apparently more frequent occurrence of pneumothorax and mediastinal emphysema in tracheotomized than in non-tracheotomized patients with diphtheric or other stenotic processes in the trachea and larynx.

Literature.

1. BAGER, CHR.: Nordisk. Med. 14: 1745 (1942) — 2. Dr. BARTELS: Dtsch. Arch. f. klin. Med. II—1867. — 3. BOYSEN, G. & F.: Acta Otolaryng. vol. XXXII fasc. 1: 50. — 4. BRAULKE, HELMUTH: Zeitschr. f. Kinderhk. 59: 181 (1938). — 5. BRUNNER, A.: Schw. Med. W. schr. 22: 1210 (1941) ärg. 42. — 6. DICK, WALTER: Beiträge zur klin. Chir. 158: 59 (1933). — 7. DOLGOPOL, VERA & STERN, E. MORRIS: Arch. Otol. laryng. XXXI: 140 (1940). — 8. FÄBER, ERIK: Dödsfallsagerne ved Differi. 1903. — 9. FIGI, F. A.: Ann. Otol. Rhin. & Laryng. 43: 178 (1934). — 10. FENICHEL, N.: J. A. M. A. 97: 20 (1931). — 11. GRAEBNER, HERBERT: Arch. Otol. laryng. XXIX: 446 (1939). — 12. GÜTERBOCK, P.: Arch. f. Path. Anatomie (Virchows Archiv) 52: 523 (1871). — 13. HABS, RUDOLPH: Dtsch. Zeitschr. f. Chir. 33: 521 (1892). — 14. Dr. HASSE: Berl. klin. W. schrift 1868 nr. 1 og 2. — 15. HOFFMANN, FRANZ: Berl. klin. W. schrift 1869 nr. 50. — 16. JERRY, R.: Dtschr. Zeitschr. f. Chir. 27: 377 (1888). — 17. KEIS, JOSEF: Münch. Med. W. schr. 81: 669 (1934). — 18. KELMANN, SARAH: Arch. of Int. Med. 24: 332 (1919). — 19. KIRSCHNER, J. J.: Am. J. Med. Sc. 196 II (1938). — 20. KJÆRGAARD, HANS: Acta med. Scand. 1932 suppl. 43. — 21. LEINER, CARL: Jahrb. f. Kinderhk. 58: 448 (1903). — 22. MICHELS, MERRIL: Arch. of Otolaryng. XXIX: 842

- (1939). — 23. MÜLLER, FRIEDRICH: Berl. Klin. W. schr. 1888 nr. 11: 205.
— 24. NEFFSON, H. & BULLOWA, G. H.: Arch. Otolaryng. XXVIII: 389
(1938). — 25. DR. SACHSE: Archiv f. Path. Anatomie 51: 148 (1870). — 26.
SAXL, OTTO & MENDEL: Zschr. f. Kinderhk. 59: 533 (1938). — 27. SCHÜL-
LER, MAX: Dtsch. Chirurgie hg. von BILLROTH & LÜTKE: Tracheotomie bd.
37 (1880). — 28. SELDÉN, R.: Nord. Med. I: 452 (1939). — 29. WIETHE, CA-
MILLO: Monatschr. f. Ohrenhk. 67: 57 (1933). — 30. WISSLER, H.: Jahrbuch
f. Kh. 150: 11 (1938).
-

A Study of the Onset and Prognosis of Nephritis in Children.

By

ÅKE FRISK and G. KLACKENBERG, Stockholm.

The present investigation was undertaken in the belief that follow ups carried out a sufficient number of years after the illness was first diagnosed, would throw light on the prognosis in the various types of onset of the disease. An American (ALDRICH) has put forward the view that the disease which develops into chronic nephritis may be diagnosed by its prodromal features. Apart from this, it has long been thought that the chronic state was always preceded by an initial acute state, even if, in many cases, this was for various reasons disregarded. Why the acute stage should later develop into chronic nephritis is not definitely known. It has been pointed out with justification that certain factors, principally neglect and insufficient care, tend to make the illness become chronic, but in many cases in spite of the strictest hygienic and dietetic bed rest, the illness develops relentlessly over a period of many years, terminating in the hopeless condition of uremia.

Pediatricians, who are familiar with the onset and early symptoms, see the tragic development less often than specialists in adult wards. It follows after years of apparent health, normal development and well-being. If the urine is tested at periodic medical examinations, there may sometimes be traces of albumin and at other times normal urine. In many cases sedimentation tests have also failed to diagnose the real and serious nature of

the illness. ADDIS' method of quantitative sediment counts is, however, of further assistance in diagnosis.

In most cases of acute nephritis the onset is sudden and striking. Some days or weeks after or during some infectious disease, the urine turns dark, reddish black or red. Even less observant parents do not as a rule fail to notice that the urine has changed in colour. After a shorter or longer period, in exceptional cases up to one or two years, the symptoms of acute nephritis disappear. Chronic nephritis — as defined by ALDRICH — is, on the other hand, discovered more by chance. During a school or other routine medical examination, or an examination on account of lack of appetite, headaches and lassitude, or swellings round the eyes, the urine is found to contain albumin. The patient's family have no knowledge of any previous infection or acute hemorrhagic state. The disease has developed insidiously and the exact time of onset cannot be fixed. The further development is, or can be, as stealthy and unnoticeable as the beginning. But sooner or later the disease reaches its final stage with uraemic symptoms. Every doctor can, however, probably testify that there exist certain cases which become chronic and result in death from uremia many years after the disease has passed through an acute hemorrhagic phase. The years between may have been comparatively free from symptoms.

ADDIS, who supports the view that nephritis always starts with an acute stage, divides it into four phases: acute, latent, active and terminal. The latent stage is often unnoticed at routine examinations of the urine, as the symptoms are negligible. The quantitative sediment count is, however, always pathological in this stage. During the active stage, the urine always contains albumin, often in large quantities, and in addition red blood corpuscles and casts. Because of the possible occurrence of edema, increased blood pressure, and lowered plasma-albumin, this stage can, in certain cases, be easily confused with nephrosis, but differs from it in the existence of red blood corpuscles in the urine. The terminal phase is the uraemic stage. It is not necessary for the disease to pass through all the stages, it may go from the acute to the active or terminal.

Most acute cases pass over and the child is again healthy. It is possible that some latent cases also clear up, but this occurs more seldom. When the disease is in this insidious phase, or just beginning the active state, it might easily appear — as ALDRICH found it — to be »primary chronic». It often happens, however, that a subject with chronic nephritis has acute hemorrhagic exacerbations in connection with infections. If the chronic nephritis had previously developed unnoticed, it appears at such an exacerbation to be the onset of an acute attack, and the subsequent development is judged in accordance with ADDIS' theory. These contradictory opinions are both well-founded. It would obviously be of great value to be able, as ALDRICH believes, to determine the prognosis in the early stages of the illness. Since, as far as we know, no investigations have been made in Sweden to throw light on this problem, we decided to make one.

This was our original purpose. The investigation has, however, gradually expanded to include an examination of the prognosis itself, where we used ADDIS' quantitative sediment count to insure that no cases of latent nephritis passed as healthy. The follow ups took place a long time, at least ten years, after the onset of the disease. This was done in order to be more certain which cases had really become chronic. No case of recovery from nephritis after so many years is known. Those who still had pathological urine suffered from chronic nephritis. In this way the problem was simpler and more lucid. Curable nephritis can still persist one or two years after the acute hemorrhagic state. ARCHIBALD found among 33 followed up cases, only two which cleared up after the ADDIS count had been pathological for 18 months. Similar results have been published by others (DE LEEUW, SNOKE, CASS).

Finally, we have examined the value of other symptoms, and studied our group of nephritic children from various points of view.

	No. of cases	No. of yrs. of observation	Recovered	Not recovered	Test made	Remarks
<i>Group 1.</i>						
ERNBERG (1911)	40 approx.	at least 16	40 (100 %)			Only 54 % of the survivors followed up
OSMAN (1925)	56	1½—22	36 (64 %)	20 (36 %)		Only increased B. P. (blood-pressure) 5 9 of these only abnormal urine
PATERSON (1926)	26	3½—5½	12 (47.5 %)	14 (52.5 %)		
BOYD (1927)	44	2—5	36 (82.3 %)	8 (17.2 %)		
ALTHOF	41	1—10	34 (83 %)	7 (17 %)		
SUNDAL (1931)	19	1—14	15 (79 %)	4 (21 %)		
LYTTLE (1929)	38	1—7	34 (89.4 %)	4 (10.6 %)		
PETRÉN (1927)	254	2—25	230 (90 %)	12 (10 %)		Scarlatina nephritis. Only increased B. P. in 8 cases. 12 died of acute nephritis.
SÄLLSTRÖM (1937)	206	1—14	173 (84 %)	33 (16 %)		Scarlatina nephritis. Only increased B. P. in 10 cases of the 33. 24 died.
SCHWARTZ (1940)	120	1—16	101 (84.1 %)	14 (11.7 %)		Only albumin 5 (4.2 %) who would have needed a longer period of obs. for classification.
<i>Group 2.</i>						
JAMES (1921)	67	9/13—16	58 (86 %)	9 (14 %)	Conc. test	Albumin only examined.
SMELLIE (1926)	16	average 16	5 (33 %)	11 (66 %)	Non-P. N. (non-protein nitrogen)	All urine tests normal but either increased B. P., hypertrophied heart or increased non-P. N.
GUILD (1931)	34	1—12	30 (88.2 %)	4 (11.2 %)	Phenol sulphatiline (- non-P. N.)	
TALLERMAN (1939)	16 (2 of original 27 were dead)	8	15 (93.4 %)	1 (6.6 %)	Phenol sulphatiline (+ non-P. N.)	

-1 non-P. N.
Phenol sulphatiline
+ non-P. N.

TALLERMAN (1939)	16 (2 of origi- nal 27 were dead)	8	15 (93.4 %)	1 (6.6 %)	Phenol sulphatiline + non-P. N.
<i>Group 3.</i>					
BOYLE et al. (1937)	25	1 $\frac{1}{2}$ -8	25 (100 %)		Patients selected from 250 cases of clinically recovered post-infectious nephritis. 1 had high Addis count but chronic pyelitis.
CASS (1939)	88	1 $\frac{1}{2}$ -5	56 (64 %)	28 (32 %)	2 patients terminal state. 3 died in acute state.
PITTINOS, CRAIG, DE SANCTIS (1941)	32	1-12	31	1	Of the 110 in original material, 4 died in initial stage (3.6%).
ARCHIBALD (1941)	33 of which 26 post in- fectious 7 non post infectious		18 (70 %)	41 (15 %)	4 (15 %) dead.
			0	3	4 dead.
<i>Group 4.</i>					
SNOKE, California (1937)	178	127 cases > 2	57 (37 %)	64 (42 %)	33 (21 %) died. 84 % of sur- vivors followed up.
SNOKE, New York (1939)	146	1-9	77 (72.6 %)	15 (14.2 %)	14 (13 %) died. 70 % of sur- vivors followed up.
MURPHY-PETERS (1941)	205	2-10	70	74	26 died. 81 % of survivors followed up. Both children and adults.

As may be seen from the last table, the same writer has arrived at highly different results in investigations carried out in the same way. His own explanation is that the differences are due to local peculiarities, the one case being in California, the other on the East Coast (Rochester).

Survey of the Literature on the Subject.

Prognosis investigations of acute nephritis have been carried out a number of times, both of scarlatina nephritis (in Sweden by SÄLLSTRÖM, PETRÉN) and of other types of post-infectious nephritis. The results have differed widely in some aspects. These great differences are undoubtedly principally due to the varying definitions of normal and healthy. In addition they are due to the length of the period of observation, and the varying views on what may be regarded as chronic. The investigations may be divided into three or four groups, namely 1) those confined to physical examination + blood pressure + routine urine analysis, 2) those which included one or more renal function tests, 3) those which also included ADDIS counts; 4) those in which repeated ADDIS tests were made over a long period might be included in a fourth group.

Unfortunately the results of the examinations cannot really be compared. They have not been reported in the same way, and must therefore be judged as approximate. In certain cases the proportion of follow ups in relation to the original number of patients has been as low as 50 to 60 %, which reduces the possibility of drawing prognostic conclusions.

The results of the investigations are given in the preceding tables.

Definitions.

Before we describe the group of nephritic children upon which the investigation is based, it is necessary in order to avoid misunderstandings, to give the criteria we have used in defining acute and chronic nephritis, nephrosis, etc. The various writers on the subject do not agree as to the basis of classification, but we have principally followed British and American practice. We made the following conditions necessary for a diagnosis of nephritis: — albumin and pathologic sediment with red blood corpuscles and casts. Blood pressure, edema and non-protein

nitrogen have naturally been noted and, in the cases in which they occur, have supported but not determined the diagnosis. Positive Heller reaction only, or pathological Addis sediment only, has sufficed in certain cases at follow ups.

The principal difference between the cases which have been called acute and those which have been called chronic has been the curability. Even if it had taken one or two years before the urine was normal, the case has been considered as acute. Those which even after ten years — the shortest length of time since the first onset — still had pathologic urine were obviously considered to be chronic. The latter is thus an incurable, progressive form. We return later to further clarifications.

By nephrosis we mean a comparatively rare disease characterized by general edema, a tendency towards a chronic state, a wavelike weight curve and pronounced albuminuria and cylinduria, but not hematuria, hypertension and non-protein nitrogen, but with cholesterol elevation and hypoproteinemia. Pathologic-anatomically it corresponds to tubular degeneration without the glomeruluschanges of acute and chronic nephritis. But one occasionally sees cases where, during the development of lipoid nephrosis, the patient is attacked by an infection which causes the appearance of red blood corpuscles in the urine and a rise in blood pressure. The nephrosis has combined with glomerular nephritis, and the result may be contracted kidney and true uremia. In other cases preceded by ascites frequently fatal peritonitis sets in (commonly pneumococci).

Material.

The material is principally made up of all cases of acute or chronic nephritis treated at the Gothenburg Children's Hospital during the years 1924—1933. The cases excluded were all those where there was grounds for suspecting that they resulted from scarlet fever, and a few patients who were not at the time normally resident in Gothenburg and whom it would, therefore, have been disproportionately difficult to follow up. Since the reason for the omission of the latter cases has no bearing on the investigation, they cannot form a source of error.

The cases of scarlet fever nephritis were omitted since extensive follow-up investigations have recently been made of such cases, and we wished to have as pure a material as possible. It may seem odd to omit such an important group of post infectious cases, but, on the other hand, the cases of scarlet fever nephritis treated at the Children's Hospital are chiefly a selection of prolonged nephritis, namely cases which have not recovered during the stay at the Hospital for Infectious Diseases. To some extent all hospital cases are a selection of those more resistant to treatment, but this source of error may be neglected here. We have, probably, been unable to avoid including a number of cases of nephritis which are, nevertheless, post-scarlatinal, namely those resulting from undiagnosed scarlet fever where the rash was insignificant or non-existent. This appears possible if one compares the frequency of nephritis patients at the Children's Hospital (excluding those definitely post-scarlatinal), with the cases of scarlatina at the Hospital for Infectious Diseases — the latter figures ought to give a good estimate of the extent of the epidemic. The comparison is naturally only a very rough one, as many other factors, which may vary independently of scarlet fever, influence the number of nephritis cases. The curves resemble one another only in places, and in any case the resemblance is sufficiently small that it can justifiably be assumed that post-scarlatinal cases are not to any extent included in the material. Conditions predisposing scarlet fever may also be so for other infections of the throat, and these, as we shall show later, form the dominant infection factor for nephritis.

The period 1924—1933 was considered to be suitable for two reasons. Firstly, because a sufficiently long time had passed since the cases left hospital, and secondly because the same doctor (WALLGREN) had had the opportunity to judge and diagnose all of them.

Cases of nephrosis have as far as possible been excluded from the material. During the early part of the period, the cases were not classified in accordance with our present practice. As a result a few cases of so-called sub-acute nephritis were classi-

fied as nephrosis and vice versa. The total number of cases in the final material was 239. Of these 229 were examined, or had died, or gave the desired information as to their state of health by letter (see the table). 175 responded, after one or more requests, and presented themselves personally for examination. Apart from renewed anamnesis and general medical examination, routine urine analysis and blood pressure, this included quantitative ADDIS sediment counts.

Those, who as the result of removal to another district or for other reasons could not come for examination, were written to (sometimes repeatedly), and answered questions regarding their present state of health, their most recent and earlier medical examinations, hospital treatment, the results of urine examinations, and on their inclination for throat infections. The hospitals and doctors in question have kindly given us the necessary information from their journals. In some cases we have also had the usual urine tests made.

The value of these contacts by letter is naturally smaller, and the results less certain in cases of latent chronic nephritis. But one may assume that at some time or other during its ten or often twenty years duration, the disease, even in the latent stage, would have been apparent. The chances that some cases of latent nephritis are concealed among those judged to be healthy are, therefore, very small.

Of the ten whom we have not been able to contact at all, 2 have emigrated to America and 8 have omitted to present themselves for examination or to answer the questionnaires which were later sent to them. This, naturally, constitutes a weakness in the investigation; we know from the public register, however, that 9 of them are still alive.

In tabular form the material is as follows:

Examined in person	175 =	} 96 % of those definitely alive
by letter	34 =	
Died of kidney disease	14	
Died of other diseases	6	
No contact	10	(9 still alive)

In order to obtain a more comprehensive group of chronic nephritis, we have included as a special group those cases from 1934—1942, where the diagnosis was confirmed by post mortems, or where at least 2 years had passed since the illness began. They comprise only 5 cases.

Method.

In the sediment tests we used ADDIS' method with a few minor changes, chiefly necessitated by the fact that we were examining out-patients. We were thus less restrictive than ADDIS prescribes as regards fluid intake. LITTLE stresses the difficulty in his work of limiting the fluid intake of children before and during tests, as this would necessitate constant supervision. The same difficulty always arises when examining out-patients. All our patients had, however, received explicit instructions in this respect. The fact that there was no control as to whether these were followed, might seem to imply a certain weakness in the investigation. This is, however, not a real weakness as the intention of restricting fluid intake is to obtain reasonable concentrated urine. ADDIS thus demands that the urine examined should have a specific weight of over 1.020, and that the reaction should be acid, since the white blood corpuscles and hyaline casts are very sensitive to and easily destroyed by alkaline solutions. We have, therefore, carefully tested the reaction and specific weight of the urine and thus obtained a sufficient guarantee that the various constituents of the urine sediment remained intact during the tests.

One source of error in this method when used for out-patients is that urine passed by women patients may now and then contain blood from the vagina. In order to eliminate this as far as possible, the examinations took place halfway between two menstruations. If the result was pathological, a further examination was made after some time. At this examination a catheter was sometimes used.

The necessary attention was paid to the occurrence of drops of fat, air bubbles and yeast fungi at the count in the counting chamber. Especially the last named may in certain cases closely

resemble red blood corpuscles. This does not, however, offer any great difficulty in differential diagnosis.

The values considered to be normal by different investigators differ widely. ADDIS himself stresses that the method is only approximate, but points out at the same time that exact values are not necessary. The main thing is to be able to differentiate the clearly pathological values. ADDIS puts the upper limit for red blood corpuscles in a 24-hour urine output at 425 000, while GOLDRING puts it generously a $1\frac{1}{2}$ million. The corresponding figures for casts are 4 270 and 9 200 respectively. We ourselves have called pathological values over 800 000 for red blood corpuscles, while the corresponding limit for casts was fixed at 20 000.

Results. The Significance of the Onset of the Disease for Prognosis.

The chief purpose of the investigation was to throw light on the significance of the onset for the prognosis, in what way the type of the first noticeable symptoms can indicate the subsequent progress of nephritis. To this end, we have divided the material into various groups. Firstly, a group of chronic nephritis where post mortem has shown typical renal changes, and secondly a smaller group where, although there was no post mortem, the illness had had a typical terminal course with uremia and hypertension. Further, a number of cases (group 3) which are still alive, but still have urine changes at least ten years after the illness was first diagnosed, and must, therefore, be classified as chronic. The final large group comprises the acute cases.

Of the 8 cases in Group 1, 5 had gradual onsets, and 2 at the time the illness was first noticed, certainly had «influenza» and diftheria-otitis respectively, but no hemorrhagic onset and no typical sediment. The 8th case — a 13-year old girl — had had pyelonephritis with urine changes since one year of age.

The following case serves as a typical example of the gradual onset: S. J. 15 years old. Erythema Nodosum 1931. Urine then normal. Afterwards healthy, apart from periodic stomach trouble for several

years, gastritis according to the doctor. On entering hospital — after ten days of weakness, headaches and lassitude — no temperature, no pains anywhere. After 4—5 days pain in the small of the back on both sides. Not infected. Urine: Heller + 3 %. Sed.: 15—20 red, hyaline and granular casts. Non-P. N. 59 mg%. B. P. 140 mm Hg. Treated at hospital with bed rest and diet for 4 months. Progressive deterioration: B. P. 160, water test worse, non-P. N. unchanged. Afterwards at home for 7 months. Thereafter taken in with uremia (B. P.: 190. Non-P. N.: 222 mg%) and died. Post mortem: Kidneys small with strongly adherent capsule. Surface noticeably pale and granular. Disappearance of the glomeruli and tubules. Parenchyma strongly fibrous. — Her illness was thus right from the start in a stage of early contracted kidney, and advanced rapidly and relentlessly to the end.

The two case histories where there was some doubt as to the importance of the previous infectious disease might will be described in detail. In all the other cases we have never had the slightest doubt as to which group they belong.

S. G. 6 years old. Treated for influenza-traces of pneumonia at the Hospital for Infectious Diseases April 1931. On arrival there Heller +. Sed.: 0 red copuscles, single granular and hyaline casts. Returned home beginning of May, but entered the Children's Hospital middle of same month with 9 % albumin, single red corp., many granular casts. P. B.: 135 mm Hg. Water test normal. Treated at hospital 4 months, continuous pathologic urine. Out-patient 5 years, each time albumin and pathologic sediment. Returned later with uremia. Post mortem: Kidneys granular and twice the size of a Brazil nut, with irregular markings and extremely narrow cortex.

E. S. 15 years old. At the Hospital for Infectious Diseases 1929 with comparatively mild diphtheria + otitis. Even first urine test there was Heller +. Sed.: white cells + bacteria. Albumin during entire month's stay. Just before X-mas 1930, pale, tired, oedematous in face. Lay in bed for 2 months with albumin and increased blood pressure. Then in connection with a sore throat had hemorrhagic urine and entered Children's Hospital where she died of uremia after one month. Post mortem: very small kidneys with parenchym scarcely a centimeter thick and without regular marking. — As may be seen, at the time the disease was discovered, the urine had neither the typical constituents of nephrosis nor acute nephritis, which makes it reasonable to assume that the patient suffered from «primary chronic» nephritis and during the progress of the disease contracted diphtheria and otitis.

In the group with no post mortem but typical terminal course, are three cases with comparatively unnoticeable onset

without symptoms. The first onset of the fourth case was unknown.

Then, of the 12 fatal cases of chronic nephritis, which we term «Primary chronic», all but one (whose onset was unknown), lacked the hemorrhagic stage of acute nephritis. Another common characteristic was that most cases were of relatively short duration. We shall later give many examples showing that it is possible for cases of chronic nephritis to be in good health for 10—20 years. If we exclude the case of chronic pyelonephritis who lived for 13 years after diagnosis, and where the etiology is known and of a quite different type from that of the others, the lifetime of the cases in this group was on the average 1.6 years, of which the longest was 5 years, which shows that in most cases the disease was rapidly fatal. The clinical symptoms indicated true uremia, mostly combined with hypertension, in some cases hemorrhagic encephalitis and enteritis. A 15 year old boy, who did not die in the hospital but some months after discharge, had a hypertension of 250 and retinitis albuminurica but no increase in non-P. N. during his stay in hospital. The result of examination of the eyes was recorded in six cases, of which 3 had retinitis, one papilledema with early secondary atrophy of the optic nerve, and two normal eye grounds up to the end, but at the same time high blood pressure and increased non-protein nitrogen. Retinitis is a symptom which very often accompanies chronic nephritis in adults. ALDRICH considers that differences between the conditions in children and adults are due to changes in growth during puberty. It is therefore worth pointing out that one of the girls with papillar changes and secondary atrophy of the optic nerve had not yet reached puberty. The remaining three were 13, 14, and 15 respectively. Albumin secretion varied considerably from a trace of albumin up to Esbach 15 %.

Passing over to group 3 (12 cases), we find the conditions quite different. Of the cases of chronic nephritis still alive, who had had the disease for at least ten years, 10 (of which 1 had luetic nephritis) started acutely and only 2 gradually. Most of them are in good health, some (8 cases) even after 15—20 years' illness. All have albumin in the urine and, with two exceptions

(in one case only 394 000 red and 20 000 hyaline casts in 12 hours, and in the other unknown), pathological ADDIS sediment. High blood pressure in 6 cases, in none of them over 180.

If we add to these the border-line cases (10) where the diagnosis of nephritis at the follow up was more doubtful, and all of which (except one) had a sudden onset, the impression that there are indeed different types of chronic nephritis is strengthened. On the one hand the case which starts without symptoms and then leads fairly rapidly to death, and on the other the secondary effects of uncured acute nephritis. This view is further strengthened if, from the entire nephritis material examined (224 cases), one collects together all those which were discovered through general symptoms or entirely by accident, and follows their progress. Out of 16 such cases only 2 have recovered, the other 14 have died or become chronic. If we assume that the etiology and the prognosis are of a different character in the two groups of the disease, the two cured cases can be explained by the assumption that the acute onset was unnoticed or treated casually by the parents.

Prognosis.

From the results of our investigation we are fully justified in stating that the prognosis for the acute, hemorrhagic form of nephritis is good. Out of a total of 230 cases where the disease started as acute, hemorrhagic nephritis, only five died during the acute stage. All five had symptoms of general infection in addition to renal damage (otitis + empyema, peritonitis + empyema, septicopyemia + empyema, septicemia + meningitis purulenta, and myocarditis + bronchopneumonia) so that one must assume that the chief cause of death was not nephritis but general infection. In these cases nephritis was but one of the symptoms. The non-protein nitrogen was increased, maximum 112 mg%, in the four cases in which it was examined. In one case it is possible to assume that the renal disease was the factor actually causing death. This one case, therefore, indicates the real immediate risk of death from hemorrhagic nephritis, i.e. 0.4 %.

We have not been able to contact 10 of the 230 cases of acute nephritis either because they have left Sweden (2 cases) or have not answered letters or presented themselves for examination (8 cases). 6 of the remaining 220 have died of other diseases (pulmonary tuberculosis, rheumatic endocarditis with chronic valvular disease, disease of the intestines, etc.). Post mortems have been made in four cases, in the remaining two we have got the diagnosis from the Death Register.

12 of 214 (= 5.6 %) still have renal changes at least 10 years afterwards, which indicates permanent renal damage. To these must be added 10 cases, which we have termed borderline, as we have not been able to determine with certainty whether or not chronic nephritis exists. 8 of them lack albumin but have pathologic sediment, and two with albumin have normal ADDIS counts. A few have slightly raised blood pressure, all are subjectively healthy, carry out their work without trouble, and two or three are sportsmen. Repeated urine tests with quantitative sediment counts would be necessary for accurate classification. If we include these in the chronic nephritis group we arrive at 10.3 %, a figure which is with absolute certainty the upper limit.

Factors Influencing the Prognosis with Acute Onset.

In 17 cases there was kidney disease in the family. This is for various reasons a minimum figure, but it is of interest to see whether there is any real connection between the nature of the disease in the family and in our patients. 8 were pairs of brothers or sisters, who were attacked by the same infection at approximately the same time and developed nephritis. The 9th is also one of a pair, but the brother was treated elsewhere. All recovered except one who died of his very acute infection. Of the 8 where one of the parents suffered from kidney disease, four became chronic after a hemorrhagic onset. The figures are low, and one is not justified in drawing any conclusions.

Hemorrhagic nephritis can now and then have a very violent onset: cramps, blindness, anuria combined with increased non-protein nitrogen. This acute uremia does not appear to influence

the prognosis. Of the 7 who had acute uremia, all lived, 6 have recovered and one classified as a border-line case. The non-protein nitrogen varied from a medium increase to over 300 mg%. In one case decapsulation was performed. Acute convulsive uremia must, of course, be strictly differentiated from true uremia. It might be worth pointing out that the 9 year old boy, who during acute uremia had as high non-protein nitrogen as 361 mg%, was not troubled by headaches or vomiting during the 9 days that the non-protein-nitrogen was above 200 mg%. He had, however, suffered from them at the onset. It is probably not the nitrogen retention as such which gives rise to these symptoms.

Tonsillectomy does not appear in this material to have been of any use as a prophylactic against becoming chronic. This may, however, be due to the fact that it is principally in cases of prolonged nephritis that tonsillectomy is performed. The percentage of uncured nephritis among those whose tonsils has been removed, usually within 3 months, is about the same as among those who had not been treated in this way. The number of cases where tonsillectomy had been performed was 45.

Of the cases of acute nephritis who had recovered by the follow up, in which it was possible to determine with certainty the time at which they had become free from albumin and where we had a measure of the amount of albumin at the onset (a total of about 150 cases), 53.5 % were free within 1 month, a further 25 % within 2 months, and the remaining 21.5 % after more than 2 months. In other words, slightly more than every 5th case of acute nephritis needed treatment for more than 2 months before being definitely free from albumin. This is, however, not the same as saying that they had recovered by that time, since erythrocyturia usually remained considerably longer as signs of renal damage.

A better measure is, of course, the length of treatment, on the assumption that the urine was free at the time of discharge. In studying this, we had to exclude those who had not recovered before discharge, or before the last tests in the out-patients' department. The figures we arrived at thus express the certain

recoveries, but are for obvious reasons minimum figures, since a number of those discharged before 2 months (in certain cases after a few weeks) were well nursed at home and lost contact with the hospital. 69 % of the now recovered cases of acute nephritis had certainly recovered from all symptoms of nephritis within 2 months. The remainder, scarcely a third, thus required more than 2 months treatment. That those who were classified during the first few weeks as rich in albumin (Esbach at least 2 ‰) required longer treatment than those with less albumin discharge, is perhaps not surprising. 45 % of those rich in albumin were ill for more than 2 months, while only 31 % of all the acute cases required the same length of treatment. The former recover more slowly but the prognosis in the long run is not worse. The average initial albumin discharge for the groups »chronic», »border-line», and »recovered» at the time of the follow up was 1.8, 2.0, and 1.9 ‰ respectively, i.e. no significant difference.

Prognosis with Lingering Nephritis (rest-sediment).

In a disease such as nephritis, where the acute stage is of comparatively long duration, it is only to be expected that many cases must be discharged before a permanent freedom from symptoms is achieved. The patients have been recommended to remain in bed at home and under the control of a doctor. In only some of the cases has this control been carried out by the doctors at the Children's Hospital, so that it was possible to obtain a picture of the further progress of the disease from the out-patients' journals. In the case of persistent sediment or traces of albumin, the principle in general has been after 2 months fruitless waiting for improvement, to try letting the patient get out of bed by degrees. If no significant relaps took place, this method was continued, and the length of time out of bed increased. It would be of interest to see how this method succeeded in the long run. Of the 18, who after being in bed as a rule for a month to half a year were allowed to get up without being free from albumin and/or erythrocyturia, 12 had completely recovered by the follow up, 5 were classified as border-line cases

or chronic, and 1 had died. $\frac{2}{3}$ of the cases which were not free from symptoms have thus recovered in spite of the fact that treatment had been given up. It may also be asked what was the condition during the acute stage of patients who still had urine changes at the follow up. These comprised altogether 21 cases. 7 of them were free from symptoms at a normal urine analysis. But, with our present knowledge of the nature of nephritis, we can assume that an ADDIS count would have shown them to be latent cases. 5 had traces of albumin and sediment, but were nevertheless allowed to get up. In 9 cases we do not know the state of the urine as it was tested by other doctors or not at all. — Conditions are to some extent different in the fatal chronic cases. Many cases had not left hospital, the disease had grown steadily worse. If they had been discharged it was only for short periods in bed at home. None of them were discharged as free from symptoms.

Previous Infections, Age, Sex, etc.

The types of previous infection are given in the table below. As respiratory infections have been classified pharyngitis, adenoiditis, otitis, cervical lymphadenitis, bronchitis, and bronchopneumonia. Subdivision of these different groups would be artificial. Otitis or lymphadenitis are not isolated complaints, bronchitis and bronchopneumonia often occur together with pharyngitis. On the other hand, we have tried to place the cases of tonsillitis into a special group. We are fully aware that the figures are only approximate, since the details given in the journals are often based on the parents' own description of the throat complaint which the child had had some weeks earlier. In the group of undefined acute infection are included such general symptoms as fever, nausea, vomiting, diarrhea, undefined pains, etc. Without doubt there are included in this group many cases which ought to be included under respiratory infections. Some cases of septicemia are also included. »Without known previous infection» includes partly those cases with insidious onset, and partly those where the infection was not stated in the anamnesis.

Respiratory infections.....	137
Tonsillitis.....	48
Impetigo, skin abscesses.....	7
Parotitis.....	2
Lues.....	1
Undefined acute infection.....	18
Without known previous infection.....	26
(including some cases with hemorrhagic onset)	

The time before the appearance of renal hemorrhage differs to a certain extent when it appears after tonsillitis or after respiratory infections. In the cases (far from all) where it has been possible to determine with a tolerable degree of accuracy when the infection and the renal hemorrhage started, the position is as follows:

	Renal hemorrhage			
	immed.	after 1 week	1—2 weeks	2—4 weeks
respiratory infection.	18	35	34	10
tonsillitis.....	1	7	18	15

If any conclusions can be drawn from this, it would appear that it takes a longer time for tonsillitis to develop into nephritis. After scarlet fever one also notices a latent period of a few weeks. It would, therefore, seem that the cause of tonsillar nephritis is to be found in an anti-body reaction against the hemolytic streptococci. In 5 cases allergic manifestations such as purpura rheumatica (HENOCH-SCHÖNLEIN) and astmatic bronchitis appeared at the same time as the sudden renal hemorrhage. This strengthens the belief that tonsillar nephritis arises in an allergic way. The capillary damage and arteriolospasm which are typical of this reaction do not only occur in the kidneys, but also in the skin (edema), the heart (valvular edema with murmurs) the serous membrane (exudation) and the brain (eclampsia).

The previous infections derive principally from the throat and respiratory organs. Such infections are most common during the autumn months when nephritis is also at a climax. 40 % start during October, November, December, while the minimum occur in July and August.

The material divided according to age and sex is as follows:

Age	Boys	Girls	Total
0—1	0	1	1
1—2	2	2	4
2—3	4	5	9
3—4	10	7	17
4—5	15	7	22
5—6	15	5	20
6—7	8	10	18
7—8	14	16	30
8—9	8	9	17
9—10.....	13	8	21
10—11.....	13	5	18
11—12.....	9	7	16
12—13.....	6	10	16
13—14.....	4	9	13
14—15.....	6	4	10
15—16.....	3	4	7
			<hr/> 239

That the largest number of cases occur during the seventh year, is probably due to the fact that Swedish children begin school at this age and are, therefore, more exposed to infections.

Comments.

Eight of those classified as healthy at the follow up have been treated for renal hemorrhage or albumin on more than one occasion. With few exceptions, they were healthy by ordinary clinical tests at the time of discharge. Freedom from symptoms may have lasted for several years, not only subjectively but also at urine tests, sooner or later, in one case 12 years after the first attack, there has been a relapse of the disease in connection with some acute infection. The following is a typical example:

T. B. ♂ 7 years. 1918 hemorrhagic nephritis in connection with suppurative lymphadenitis. Healthy till 1923 when renewed renal hemorrhage without definite infection, but with enormously hypertrophic tonsils. Healthy at discharge after four months. Renewed albumin

in 1933 after a septic throat, treated for several months at the Sahlgren Hospital. Medical examination for army, 1936, 0 albumin. Still healthy at later examinations, and at the follow up.

Had the follow up only comprised a Heller test one would have suspected that this was a case of latent chronic nephritis. But we considered that on a basis of the tests made he could be termed healthy. There is, of course, nothing to hinder a new relapse in connection with infection.

The following case was slightly different. C. A. R. ♂ 15 years. 1925 renal hemorrhage, treated 3 months. Trace of albumin at discharge. 1926—1932 albumin several times, usually after colds. Treated at the Garnison Hospital, Stockholm, four months 1932. After this always neg. Heller in spite of fevers. Normal urine at follow up. That is albumin on and off for seven years, followed by recovery lasting 12 years.

In this case it is impossible to decide whether the renal damage cleared up at some time during the 7 years or whether the exacerbations affected slightly damaged kidneys. Were this the case, and there is much in favour of this interpretation, it would show that complete recovery, not only freedom from symptoms, can occur even after many years. The limit for this has previously been fixed by ARCHIBALD, SNOKE, CASS and others at 2 years, but the accuracy of this may justifiably be questioned.

The following case is more open to doubt: A. A. ♀ 10 years. 1924 in bed 5 weeks with albumin. Onset unknown. Patient healthy for 2 years (urine tests?). 1926 without known previous infection troubled by lassitude — edema — renal hemorrhage. Hospital treated 3 1/2 months. Continued treatment at home for many months but albuminuria remained six months later. On examination 4 years later healthy. 1932 renewed albumin and hematuria without manifest infection. Treated 3 months but continuous albumin for 4 years, when deemed healthy. Controlled 1943: 0 albumin. At follow up 1944 Heller neg. and normal Addis sediment. But the output of urine during the 12 hours of the test was as much as 1010 cc (sp. w. 1008), i.e. an altogether unusually large output. B. P.: 150 mm Hg. We would include her in the group of border-line cases, in spite of the fact that albumin has not been found for 7 years and that the Addis sediment count was not pathologic.

In latent nephritis the exacerbations occur more quickly and are generally preceded by milder, often disregarded infections, than is the case in renewed attacks of definitely cured nephritis. The exacerbation in the chronic case is often hemorrhagic after the most insignificant infection. The »primary chronic», on the other hand, starts only exceptionally with hemorrhage. The exceptions probably consist of cases where an infection attacks a person already suffering from undiagnosed »primary chronic» renal damage. To decide at the actual sick-bed what form of the disease one has to deal with can be very difficult. It is of great importance to obtain an accurate and comprehensive anamnesis, to check up on a possible previous renal hemorrhage, transient eye edema, general state of health during the last few months before the present disease, and the type and time of the latest infection. Taking all these factors and the clinical examination into consideration one generally comes pretty near the correct prognosis, i.e. more as regards the fatal result than the duration. The prognosis in the most common combinations may be set out as in the following table:

Previous State of Health	Infection	Renal Hemorrhage	Prognosis
normal	+	+	good
normal	—	+	probably good
normal	—	— (but hemorrhage often overlooked)	probably bad
reduced	—	+	probably bad
reduced	—	—	bad
previous hemorrhage or albumin	+	+	depends on the circumstances of the first occurrence
ditto	—	+	ditto, but probably bad

Summary.

The investigation comprised a study of 239 cases of nephritis, of which 96 % of those still alive 10 to 20 years after the first hospital treatment, were followed up. In addition to the ordinary tests, quantitative sediment counts by ADDIS' method were made. 90 % of the acute cases of nephritis, most of whom had had a hemorrhagic onset, had recovered, slightly more than 5 % had permanent renal damage, and somewhat less than 5 % were border-line cases, where further investigation would have been necessary for definite classification.

The form of the onset seems to be of the utmost importance for prognosis. An unnoticed insidious onset was combined with bad prognosis. This form of the disease, termed «primary chronic», led relatively quickly, in all cases within five years, to death. This type of onset is not common, only 11 cases in the total material. The «secondary chronic», on the other hand, influenced the general state of health surprisingly little over a long period (10—20 years). Acute convulsive uremia and the extent of the initial albumin did not influence the prognosis, neither did tonsillectomy.

(We should like to take the opportunity to thank chief doctors Med. Dr. FAXÉN and ÅKERRÉN, Gothenburg, whose valuable help rendered possible the technical side of the investigation, and to express our gratitude to colleagues throughout Sweden for their kindness in answering our questionnaires.)

Literature.

ADDIS, J. A. M. A. 85: 163 (1925). — —, Journal of Clinical Investigation 2: 409 o. 417 (1925/26). — ALDRICH, Am. J. Dis. Childr. 41: 766 (1931). — ALDRICH & BOYLE, J. A. M. A. 100: 1979 (1933). — ARCHIBALD, Arch. Pediatr. 58: 555 (1941). — BOYD, Canad. M. A. J. 17: 894 (1927). — BOYLE & ALDRICH & FRANK, Am. J. Dis. Childr. 53: 1167 (1937). — CASS, Arch. of Dis. Childhood. 14: 137 (1939). — ERNBERG, Nordiskt med. arkiv (1911). — FANCONI, Schw. Med. Wochenschrift 63: 412 (1933). — GACHET, Am. J. Dis. Childr. 61: 1175 (1941). — GELDRICH, Jahrbuch für Kinderheilkunde 141: 249 (1934). — GUILD, Bull. J. Hopkins Hospital 48: 193 (1931). —

25—46416 *Acta paediatrica*. Vol. XXXIII

HINZE, *Jahrbuch f. Kinderheilkunde* 148: 177 (1937). — JAMES, J. A. M. A. 76: 505 (1921). — DE LEEUW, *Acta Pædiatrica*, suppl. 1, art. 2 (1937). — LYTTLE, J. *of Clin. Investig.* 12: 87 (1933). — LYTTLE & ROSENBERG, *Am. J. Dis. Childr.* 38: 1052 (1929). — OSMAN, *Guys Hosp. Rep.* 75: 306 (1925). — PATERSON, *Archives Dis. Childr.* 1: 103 (1926). — PETRÉN cit. after SÄLLSTRÖM. — PITTINOS & CRAIG & DE SANCTIS, *J. A. M. A.* 117: 1855 (1941). — SCHWARZ & KOHN & WEINER, *New York State J. of Med.* 40: 409 (1940). — SEEGAL & LYTTLE & LOEB et al. *J. Clin. Investigation* 19: 569 (1940). — SMELLIE, *Brit. Med. J.* 2: 37 (1926). — SNOKE, *Am. J. Dis. Childr.* 53: 673 (1937). — —, *J. of Pediatr.* 14: 111 (1939). — SUNDAHL, *Tidskrift f. Norske Lægeforening* nr 3 (1931). — SÄLLSTRÖM, *Acta pædiatrica*, suppl. 1, art. 2 (1937). — TALLERMAN, *Lancet* 1: 242 (1939).

Acute Macrocytic Anemia in the Newborn¹ **(with Special Reference to its Relation to Erythroblastosis Foetalis).**

By

SVEND HEINILD.

Introduction.

While anemia in infancy is of frequent occurrence, anemia in the newborn — more strictly defined within the first two weeks of life — is a very rare phenomenon apart from the classical erythroblastosis foetalis (hydrops, icterus gravis, anemia neonatorum) which, as a matter of fact, is not particularly common either. In this period of life, however, there sometimes appears a morphologically well-characterized, macrocytic, hitherto idiopathic, form of anemia that has several features in common with the erythroblastosis and which, according to our present view, cannot be entered in the system. We have had an opportunity to observe some cases of this form of anemia, which has given rise to the publication of this paper.

Historical Data.

In 1911 FINKELSTEIN mentioned a type of anemia in the newborn characterized by a pronounced reduction in the hemoglobin percentage and in the red cell count. The first thorough description of such a case was given by ECKLIN in 1919, and this was followed by other papers by DONALLY (1924), SUSS-TRUNK (1924), SANFORD (1925), and in 1931 ABT was able to gather 15 cases of this kind from the literature. At the same

¹ Read before the Danish Society of Pediatrics, October 3, 1945.

time, BLACKFAN, BATY and DIAMOND published a monograph on the disease. As far as I have been able to find out, the first time it was the subject of detailed mention in a comprehensive textbook of hematology was in 1937 when KRACKE and GARVER dealt with it under the designation: Idiopathic macrocytic anemia of the newborn.

Definition and Delimitation.

The features characteristic of this form of anemia, according to the authors' mentioned above, are as follows: The child is born of healthy parents, after normal pregnancy, often preceded by several births of healthy children. In the course of the first two weeks of life (as reported, from the 1' to the 17' day) an extreme degree of anemia (the children are characterized as »pale as a sheet») develops rather acutely, with or without accompanying jaundice (thus jaundice was present in 5 of the cases gathered by ABT).

The children are afebrile and, as far as that goes, they give no impression of being very ill except for the anemic features.

Often the anemia shows a hemoglobin percentage between 10 and 30. It is a macrocytic and hyperchromic anemia, apparently involving a specific disease of the erythron, the white blood count and the platelet count being normal or, often, even slightly increased. The reticulocyte percentage is about normal, 2—4 %. In view of the age of the patient the nucleated red cells in the peripheral blood are relatively few in number, often making only a few percent — entirely different from the findings in the classical erythroblastosis. This is a striking feature as otherwise enemas of the newborn have a tendency to be erythroblastotic (KUGELMASS).

The following negative characteristics are decisive: there is no evidence of any birth injury, hemorrhage or hemorrhagic diathesis, no infectious stigmata in the mother or child (including signs of syphilis or tuberculosis), no evidence of prenatal intoxication in the mother (*e.g.*, lead, acetanilide, benzol) although several case histories have been gone through thoroughly with a particular view to this point.

Most often the lesion terminates in recovery — as far as that goes, without treatment as well as with employment of therapeutic measures, among which blood transfusion is the only one to be considered — still some children die in the acute phase. The restitution is complete. Children that are reexamined for several years have never shown any relapse, but always a perfectly normal blood picture. Thus the course of the disease has the character of a reaction.

From this it is evident that this disease has some points of resemblance to the classical erythroblastosis, from which it differs though as far as the hematological aspects and prognosis are concerned. It cannot be classified under *Morbus hæmorrhagicus neonatorum*, congenital hemolytic icterus or aplastic anemia. Also the so called aregenerative hypoplastic anemia (DIAMOND and BLACKFAN) is out of the question. Leukosis and simple nutritional anemia exclude themselves.

Many different names have been suggested to this form of anemia. For the present, like ABT, we find the most suitable term to be *anemia in the newborn*, perhaps with the addition: *macrocytic* — because various anemias have a tendency to show certain fundamental morphological characteristics.

Writer's Cases.

The present material comprises 3 patients, placed among their siblings as follows:

No. 1, male, 11 years, well

» 2, female, 8 » »

» 3, male, 6 » »

» 4, male, twin A, died at age of 3 days = Case 1

» 5, male, twin B, 4 years, well = Case 2

» 6, }

» 7, } abortions in 2'—3' months

» 8, }

» 9, male, died at the age of 6 days = Case 3.

At the birth of the last child the father and mother were

respectively 32 and 36 years old; both were perfectly well and had never been hospitalized. The family histories of both the father and mother were negative, especially as far as diseases of the blood were concerned. Venereal infection was denied, and the Wassermann test was negative in both parents (performed on admission of the last child). Complete hematological examination gave altogether normal findings. In addition, the blood grouping of the parents turned out as follows:

	Father	Mother
Blood group:	0 MN Rh (+)	0 N Rh (-)

¹ In the blood of the mother a very strong anti-Rh agglutinin was demonstrated.¹

Case 1.

Male, 3 days old, twin A. Birth by natural delivery, easy, vertex presentation. Weight at birth 3 000 g. No asphyxia. On the 2' day of life, an icteric hue was noticed. On the 3' day he was strikingly flabby and poorly, undoubtedly anemic. He was admitted to Dep. B, Copenhagen County Hospital, but died 3 hours after admission. No premortal examination of the blood was made. Autopsy revealed merely icterus neonatorum and intracranial hemorrhage.

Case 2.

Male, 7 days old, twin B. Admitted to Dep. G, the Rigs-hospital (case record 547/40).

Birth by delivery in breech presentation. Weight at birth 3 450 g. No asphyxia. As in Case 1 an icteric hue was noticed on the 2' day of life. The jaundice increased markedly during the following days, though without making the patient so exhausted as his twin brother. He was given cow's milk exclusively, which he took very well. On the 7' day of life he was admitted to the University Clinic of Pediatrics.

Objective Examination. General condition fairly good, crying

¹ These examinations were kindly performed by Dr. FREIESLEBEN, the State Serum Institute.

fairly loud; not particularly poorly. Pronounced universal jaundice. No enlargement of the liver and spleen.

Blood group: 0.

Prothrombin time (LARSEN & PLUM): normal.

Urine: no albumin; urobilin + (weak); urobilin 0.

An abstract of the blood examinations during the two months' hospitalization shows:

	10/10	22/10	27/10	31/10	11/11	3/12	17/12
Hb. %.....	53	44	49	68	70	76	89
R. b. c.....	1.86	1.06	1.69	2.53	3.78	3.69	4.97
Color index.....	1.43	2.09	1.48	1.36	0.93	1.04	0.89
Retic. %.....	2	2.5	1.4	1.8	4.0	1.6	2.0
Eosin. leuk.	540					1 734	854

Course. As is evident from the tabulation above, the pronounced hyperchromic anemia was replaced by a normal blood picture with distinct eosinophilia (normally the limit for eosinophilia is set at 400 cells per cmm). The icterus subsided within 3 weeks, and the patient was thriving well, appearing perfectly well at his discharge. Reexamination, 4 years later, showed a normal hematological picture. In the intervening period the boy had developed normally in every respect.

Case 3.

Male, 6 days old. Dep. G of the Rigshospital (case record 111/45).

Birth by natural delivery at term. Weight at birth 3 500 g. No asphyxia. The mother had had some tendency to hemorrhage during the first half of pregnancy, when undoubtedly she was anemic, while she was feeling perfectly well during the latter half of pregnancy. The child was not given breast milk at all. Even at the time of birth he was noticed to be yellow, and the icterus persisted though it was rather decreasing during the following days. On the day before admission (*i.e.*, the 5' day of life) a couple of suggillations were noticed in the face and on the trunk, and on the following day the patient suddenly became very pale, with cool extremities, on which account he was hospitalized at once.

Objective examination: Moribund on admission. Skin wax-pale, with a slight yellowish hue. Temperature 32.3°. Liver palpable 2 cm below the costal margin. Spleen not palpable. A few suggillations scattered about but no petechiae.

Blood examination was performed at once, giving the following results: Hemoglobin percentage: 20. Prothrombin time (LARSEN & PLUM): 32 sec. (normally 22 sec.). Blood group: 0. Blood smears: Myelocytes 2.5 %, metamyelocytes + staff nuclears 3 %, segmented leukocytes 5 %, lymphocytes 87.5 %, non-terminable 2 %.

There were 1.5 % nucleated red blood cells per 100 white cells; and there were numerous platelets in the smear.

Micrometry showed an average diameter of the red blood cells of 8.7 μ .

While preparations were being made for blood transfusion, the patient died, in less than 2 hours after admission.

Autopsy revealed no particular abnormality except extreme anemia.

Histological examination (Professor ENGELBRETH-HOLM):

Liver normal in structure and well preserved. Between the normal liver cells only very few immature blood cells are seen, apparently considerably less than are found normally shortly after birth. The blood in the vessels is characterized by large immature nucleated cells. No inflammatory or other pathological processes are seen in the liver tissue. A good deal of bile pigment is seen.

Kidney: Only normal features are seen. No interstitial accumulation of cells is seen anywhere; no sign whatever of hemapoiesis — not in the perirenal adipose tissue either.

Myocardium: Quite normal conditions without any infiltration.

Spleen: Configuration somewhat effaced; still the lymph follicles can be recognized. The pulp, which is rich in blood, contains but scanty nucleated cellular elements, and the amount of hemapoietic tissue is rather less than normal.

Thymus: Quite normal conditions, without erythroblastotic or myeloid foci. A few myelocytes are seen — just as normally.

Bone marrow: Because of too strong decalcification, the specimen is partly a failure. The marrow is exceedingly rich in cells, mostly mature, rather large, round cells; no fat cells.

Conclusion: *No erythroblastosis foetalis is present, as erythroblastotic foci outside the bone marrow are absent. The total amount of erythroblasts appears to be smaller than normally, but nothing decisive may be said about it.*

Discussion.

Here we meet with a case history which clinically is typical of erythroblastosis foetalis, including the fact that the mother in her blood shows even a very strong anti-Rh. agglutinin after the last parturition. The case history includes first some normal pregnancies with normal children (3), but with the fourth pregnancy an «X» enters the picture. For one thing, it is a twin birth, and both twins present a severe degree of anemia. One twin dies on the 3' day of life; the other recovers from his hyperchromic anemia in the course of some months (with a striking eosinophilia). After this, the blood state is normal, and there is no tendency to relapse.

Then the mother has three abortions (in the 2'—3' month) and finally a child born on term that dies with extreme anemia on the 6' day of life. This is also an instance of macrocytic anemia.

Only one feature — though the decisive link in the chain — is lacking, namely: *Hematologically and histologically the last child should have presented the picture of erythroblastosis foetalis — but this was not the case.*

The differential diagnosis has been mentioned under «Definition and Delimitation». Here it can only be a question of erythroblastosis foetalis or the so-called idiopathic macrocytic anemia in the newborn. As is well known, the theory of isoimmunization (LEVINE, KATZIN & BURNHAM) for explanation of the origin of erythroblastosis foetalis is as follows: In the Rh-negative mother the Rh-positive fetus induces the formation of an agglutinin that diffuses into the circulation of the fetus —

though perhaps an increase in the permeability of the placenta is prerequisite (POTTER) — where it gives rise to increased destruction of the fetal blood cells, resulting in increased hemapoiesis. In the newborn as a rule such a reaction becomes erythroblastotic, whereas in older individuals it has a tendency to become hypoplastic or even aregenerative (KUGELMASS).

Now, however — as often happens when a new and apparently plausible theory is advanced — it has been found that the iso-immunization theory hardly may be able to explain all the cases entered under the syndrome erythroblastosis foetalis (HERBERT C. MILLER). For this syndrome is more complicated than assumed previously. Thus, among others, cardial, adrenal and hepatic cases find no satisfactory explanation in the theory mentioned. Furthermore, the syndrome may be encountered also in other diseases — *e.g.*, syphilis, prenatal infections, congenital obliteration of the bile duct. Perhaps a small group of cases may be due to sensitization to the special group factors M, N and P — but this event has not been described yet, merely ventilated in an editorial article in the *Lancet* (247—602—1944).

It is further to be mentioned that also before LEVINE and collaborators advanced their theory a hemolytic anemia in the newborn *without icterus* was recognized; pathologic-anatomically this condition corresponds to erythroblastosis foetalis, though without peripheral erythroblastemia — perhaps because the liver is able to eliminate the bilirubin as quickly as it is formed (KRACKE & GARVER). Like PARSONS & HAWKSLEY, moreover, it is difficult to imagine how the exquisitely acute anemia described might arise if it were not to be ascribed either to loss of blood or to hemolysis.

If now we look for a synthesis back of these apparently conflicting facts, it seems most likely to be this: that undoubtedly there is some relation between the reactive phenomenon of serological character which erythroblastosis constitutes in most of the cases and the above-mentioned idiopathic macrocytic anemia in the newborn. Our case resembled erythroblastosis foetalis both anamnesticly, clinically and serologically, but not hematologically and histologically, and hence it can be entered only

under the last-mentioned diagnosis. It seems quite obvious to imagine that the so called aregenerative, hypoplastic, anemia in infants (DIAMOND & BLACKFAN) merely represents a chronic form of the same lesion in which the patient for some reason or other has not passed the reactive stage (note, for instance, that the child described by HØYER under this diagnosis was »very pale and white» at birth). Indeed this lesion too is exquisitely an »erythronic affection» with the leukopoiesis and thrombopoiesis preserved.

It is worth considering if the classical immunization to Rhesus antigen (as actually demonstrated in our last case) might not be able also to elicit other reactions besides just a typical erythroblastotic anemia. On the other hand, we know that this form of anemia may be elicited by various factors that apparently have nothing to do with Rhesus immunization (*e.g.*, congenital syphilis and congenital atresia of the bile duct).

For the present, all cases observed ought to be published with all appertaining data so complete as possible. Possibly — and, I think, probably — the final explanation will prove to be of serological nature.

Summary.

An account is given of a family in which 3 normal parturitions with normal children were followed by 5 unsuccessful pregnancies, partly with abortions, partly with extreme anemia in the newborn within the first days of life. The parents did not have syphilis. The anemia was of macrocytic character, and in 2 of the 3 cases it terminated fatally, while in one case there was complete clinical and hematological restitution. One of the cases is described in detail, with autopsy findings. Clinically and serologically (the mother is Rh-negative, but with a very strong anti-Rh agglutinin) this case reminded of erythroblastosis foetalis, but the hematological and histological findings spoke decisively against this diagnosis. On this account the case is taken to be an instance of acute macrocytic anemia.

The relation between the two diagnoses is discussed.

References.

- ABT, A. F.: *Am. J. Dis. Child.* 43: 337, 1942. — BROMAN, B.: The Blood Factor Rh in Man. *Acta pædiatrica* 31, Suppl. II, 1934. — DIAMOND, L. K. & BLACKFAN, K. D.: *Am. J. Dis. Child.* 56: 464, 1938. — DONNALLY, H. H.: *Am. J. Dis. Child.* 27: 369, 1924. — ECKLIN, T.: *Monatschr. Kinderheilk.* 15: 425, 1919. — FINKELSTEIN, H.: *Berlin. Klin. Wehnschr.* 48: 1829, 1911. — HEY, G. J.: *Ugeskr. f. Læger.* 107: 245, 1945. — HØYER, K.: *Nord. Med.* 13: 1097, 1942. — KRACKE & GARVER: *Diseases of the Blood and Atlas of Hematology*, Philadelphia, 1937. — KUGELMASS, I. N.: *Blood Disorders in Children*, New York, 1941. — MILLER, H. C.: *Year-Book of Pediatrics*, Chicago, 1944. — PARSONS, L. G., J. C. HAWKSLEY & R. GITTINGS: *Arch. Dis. Child.* 8: 159, 1933. — POTTER, E. L.: *Year-Book of Pediatrics*, Chicago, 1944. — SALOMONSEN, L.: *Acta pædiatrica*, 32: 110, 1945. — SANFORD, H. N.: *Am. J. Dis. Child.* 30: 19, 1925. — SUSSTRUNK, G.: *Zeitschr. f. Kinderheilk.* 38: 587, 1924.
-

Paroxysmal tachycardia in infants.

By

EDGAR MANNHEIMER M.D.

The following case of a three weeks old infant, has many interesting aspects. First, there is an acute, perilous illness, which demands immediate diagnosis and treatment; secondly, it appears from the literature that those cases, though not usual, have so much the same symptoms that they could be brought together in a limited clinical picture.

To begin with, a short description of the case in question:

A three weeks old boy arrived at Kronprinsessan Lovisa's Children Hospital, Stockholm, 4.8 1945, he weighed at birth 4 200 g, he was nursed five times a day and developed normally (926/45). When he arrived his weight was 4 120 g. The mother told me that the day before arriving she had seen a pediatrician as the child had a cold and that the doctor in question stated that the frequency of heart was about 200 beats a minute. During the examination, however, the tachycardia had diminished to about 140 beats a minute.

The day the mother brought the child in she noticed that it was not normal. The respiration was violent, its lips were blue, it did not want to get nursed. The temperature in the morning was 36.3° , in the evening at 8 o'clock 35° . The doctor on duty recommended that she immediately contacted a children hospital.

On his arrival, the patient was suffering from a puffing respiration and clear cyanosis of the lips. From an examination of the inner organism nothing was to be found besides a moderate tachycardia. The patient recovered after oxygen and stimulus. The first diagnosis given in this stadium was capillar bronchitis in spite of the negative pulmonary finding. On account of this sulfadimin was given as a massive dose.

During the three following days, the general state obviously declined. The cyanosis and the dyspnoea were increasing, and the patient could not go on without oxygen. Two days after his arrival penicillin treatment was used, and after three days $\frac{1}{4}$ mg astrobain without any visible effect.

On the fourth day, 8.8 the general state was very bad, with deep cyanosis, dyspnoea and a tachycardia that could hardly be counted. Electrocardiogram showed 300 beats a minute. Besides there was a liver enlargement, coming down to the umbilical plane. At 13.30 8.8 $\frac{1}{8}$ mg neostigmin was given subcutaneously. At 15, i. e. $1\frac{1}{2}$ hour after the injection the attack had subsided. The pulse was at that time 140 beats a minute and the patient's state improved immediately in a very striking way. The general state became much better and cyanosis and dyspnoea disappeared. The patient was nursed and went on very well without oxygen. The liver reduced quickly and was smaller the same evening. The reduction continued to such an extent that the same day the patient left the hospital three weeks later, 29.8, the liver was palpable at arcus. The diagnosis was paroxysmal tachycardia with »Vorhofpropfung» and acute heart decompensation.

Thereafter the patient developed well until 21.9, i. e. nearly a month after he was discharged, when he came back with a relapse. The relapse was almost a copy of the first attack. The difference was that the diagnosis now was clear immediately and for this reason the congestive heart failure did not get to as high a degree as at the first attack. The pulse frequency was as before 300 beats a minute. This time neostigmin was given in the same dose as before ($\frac{1}{8}$ mg). One hour later no effect was evident and for this reason one did not dare to wait any longer, so the patient got 0.1 mg g-strophantin and coffein, which stimulated the patient to a better general state. However, it did not influence the tachycardia. Two hours later new neostigmindose was given ($\frac{1}{8}$ mg). After 20 minutes the change came but at the same time symptoms of over-dosage, with a heart frequency of 120 beats a minute, unequal and bumpy respiration and a beginning pulmonary edema (moist and dry rôles). Coffein and atropin (counter-poison against neostigmin) were given with good result, and the patient recovered in the same way as after the first attack.

After five hours a new short attack began. Neostigmin was given in the same quantities and 20 minutes later there was a change to normal pulse frequency.

Hereafter a continuous neostigmin dose was commenced (1/10 mg per os two times daily). Hereafter the patient has developed normally and there has been no more new relapse.

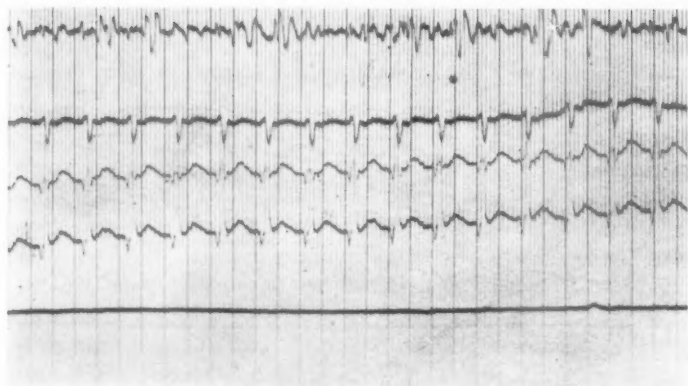


Fig. 1.

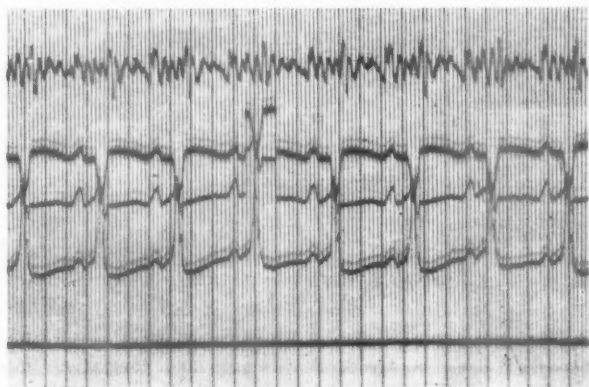


Fig. 2.

Electrocardiogram:

Fig. 1 shows electrocardiogram during the attack of paroxysmal auricular tachycardia. Frequency 300 beats a minute. Sinus rhythm.

Fig. 2 5.8. shows electrocardiogram after change to normal frequency. The electrocardiogram is pathological with atypical QRS-waves. The looks of the R-waves indicate strongly preexcitation. Enlarged P-waves. Depressed S—T intervals in leads 2 and 3. Probably acute severe myocardial damage with pronounced congestion.

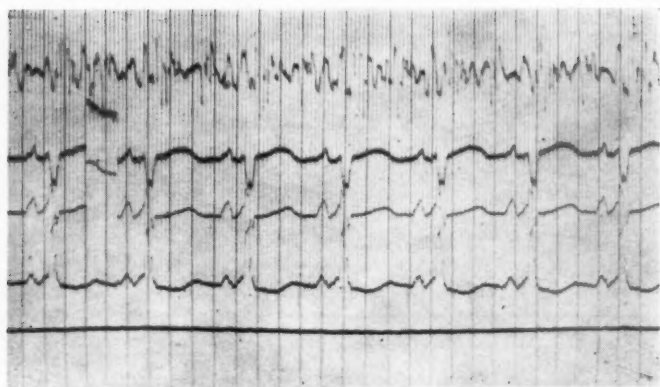


Fig. 3.

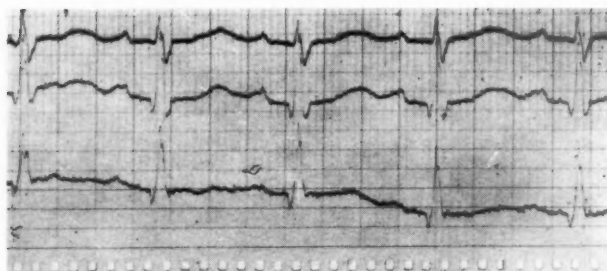


Fig. 4.

Fig. 3 15.8. Electrocardiogram and phonocardiogram show still very marked signs on myocardial damage and congestion. Amongst others a strong auricular sound has appeared, S—T intervals depressed and arcformed.

Fig. 4 shows the electrocardiogram 12.10 1945, i. e. after the second attack and the preexcitationphenomenon has disappeared. The P-waves are smaller. The T-waves now start getting more pronouncedly positive and the S—T intervals are normal. The myocardial damage is healing well.

X-ray of the heart 8.8 1945 shows a slight hypertrophia of the left ventricle and an easy bulging right hand contour. At renewed X-ray examination 9.8—21.8 1945 unchanged picture.

X-ray of the stomach 8.8 showed an enlarged liver, the lower edge of which is on level with the third lumbal vertebra.

It is consequently the question of a three weeks old boy with relapsing attacks of paroxysmal tachycardia and »Vorhofspringung» which have caused acute heart decompensation with pronounced congested liver, cyanosis, dyspnoea and bad general state. One suspected at first capillar bronchitis and the patient was given both sulphonamide drug and penicillin. Neostigmin in big doses seem to be able to cut the attacks. The neostigmin was at least at the first attack directly life-saving. Continual treatment with small neostigmin doses per os are used. No relapse has thereafter occurred. The time of observation, though, is too short — only three months — in order to make definite conclusions possible. The child has been rapidly cured after the attacks and seems to develop normally.

J. F. CHRISTENSEN has in 1944 described two of his own cases and also he has made a synthesis from the literature of the now known cases. The author claims that 37 cases of children under one year of age have been published up to the present time. The most of these cases have shown a picture which in essential parts is in accordance with the above related. HUBBARD, who has told about nine cases, has noticed no less than six during one year. The diagnosis very often has been made first at a very late stage when the heart decompensation has become absolutely clear. The origin of the illness is not clear. Infections, hypoglycaemia, rheumatical carditis, congenital heart defect etc. have been discussed. In most cases one does not find but that the nervous control of the heart has been strained.

The prognosis seems on the whole to be good in spite of that fact that 6 of the up till now known 37 cases died. Among these, most cases had a congenital heart defect or other organic illness as cause of death. However, I have to agree with CHRISTENSEN, who points out that the extreme, perilous state, which these patients show, makes it probable that some infants who die from unknown causes are dying of non-diagnosed attacks of paroxysmal tachycardia, JÖRGENSEN has in 1945 pointed to one of CHRISTENSEN's cases. The electrocardiogram shows in this case, as in my own, clear signs of preexcitation. The criteria of preexcitation which JÖRGENSEN points out are not always reliable. He demands

according to ÖHNELL a broadening of QRS to over 0.10 seconds and P—Q under 0.12 seconds. This holds without doubt true of adults, but with children, and especially with infants, it is another case. A P—Q interval under 0.12 seconds is an absolutely normal phenomenon with children under one year. Further it is evident that the QRS-wave, which is very much shorter in small children than in older ones and adults, must be considered pathological already when the values are less than 0.10 seconds. The criteria on small children consequently must be used in accordance with the normal values for the age in question. The only sure sign of preexcitation we have up till now is the R-waves appearance with the cut off on its ascending part. This change is to be found in the CHRISTENSEN's case number 2 — the same as in JÖRGENSEN's case and in the above described. The change is of interest because a big part of the preexcitation cases (accordingly to ÖHNELL, 70 %) have attacks of paroxysmal tachycardia. On the other hand one quite often finds cases of paroxysmal tachycardia where sure signs of preexcitation are missing.

This case has its special interest, as the last electrocardiogram (fig. 4) shows that the preexcitationphenomenon has disappeared. Probably it is a question of a so-called pseudonormalisation (compare with ÖHNELL). If it should be the question of a genuine normal state it should give countenance to the notion that the congenital extra connection between auricle and ventricle, which caused the preexcitation, now has disappeared and has been replaced by normal conduction.

The continued course ought to be a help to the settlement of the question as to which of those two possibilities is the actual one.

Finally some words regarding the treatment. CHRISTENSEN, HUBBARD and others have proposed strophanticus or digitalis treatment as well during attacks as during free intervals. However the effect is doubtful and it is always precarious to be obliged to subject the heart of an infant to a long digitalis treatment.

A more causal therapy has been used by STARR and later on by WRIGHT, WALSH and SPRAGUE amongst others. Through

injection of mecholyl (acetylcholine derivation) one has perceived a strong vagal effect, which cut the attack quickly. At overdosage atropin has had momentary effect. The disadvantage of using mecholyl is its rather pronounced toxic effects as vomiting, uneasiness, violent diarrhoea. Generally seen the neostigmin, which I happened to use in this case, the prostigmin has earlier been useful at adults (WALDMAN and MOSKOWITZ) does not seem to give such symptoms. At overdosage atropin seems to have a good effect here. For that reason, with that uncertainty one always feels when the experience is limited to one single case, I wonder if the neostigmin were as effective a drug both during as between the attacks of paroxysmal tachycardia of infants.¹

Summary.

One case of paroxysmal tachycardia at a 3 weeks old boy is described.

Symptoms: Pronounced tachycardia, bad general state, cyanosis, dyspnoea, enlargement of the liver. The diagnosis is made with the help of electrocardiogram. The therapy has been neostigmin injections, and during the free intervals, neostigmin per os as far as could be seen with good effect. The prognosis for this specific case seemed to be good with this treatment, but the danger of relapse makes the therapy a bit uncertain. CHRISTENSEN in 1944 had made a synthesis from the literature of 37 cases. The prognosis seems also in these cases to be good, when it has not been the question of organic heart diseases. The very bad general state makes it plausible that some cases of death of infants with uncertain diagnosis would be blamed on non-diagnosed attacks of paroxysmal tachycardia. The treatment has earlier consisted of digitalis or strophanthus. However, the effect has not been reliable. Mecholyl also was used. This drug seems to have sure effect but to give more toxic effect than the neostigmin, which was used in this case.

¹ Neostigmin is manufactured by LEO C:o Hälsingborg, Sweden. It is of the same chemical structure as Prostigmin Roche.

Literature.

CHRISTENSEN, J. F.: Nordisk Medicin 18, 797, 1944. — HUBBARD, J. P.: Am. J. Dis. Child. 61, 709, 1941. — JÖRGENSEN, J.: Nordisk Medicin 27, 1655, 1945. — STARR, J.: Am. J. M. Sc. 191, 210, 1936. — WALSH, B. J. and SPRAGUE, H. B.: Am. Heart Journal 20, 111, 1940. — WALDMAN, S. and MOKOWITZ, S. N.: Am. Int. Med. 20, 793, 1944. — WIGERS, F.: Personal communication. — WRIGHT, F. A.: Am. J. Dis. Child. 56, 1334, 1938. — ÖHNELL, R.: Acta Med. suppl. 152. Norstedts, Stockholm, 1944.

Appendix: The 16th of Januar 1946 another boy, three weeks old was admitted to our clinic with the diagnosis of paroxysmal tachycardia (73/46). This case did not show any signs of marked congestion. The liver was but slightly enlarged and the patient was in good general state even during attacks. In the hospital he steadily changed from attack to free interval. At the attack the heart frequency was 240 beats per minute and at free interval 150 beats per minute. After neostigmin subcutaneously $\frac{1}{16}$ mgr = $\frac{1}{8}$ ml twice daily no attacks appeared. Neostigmin per mouth did not show any definite effect. Accordingly we gave digitalis (cedilanid) and after that no further symptoms of paroxysmal tachycardia have manifested themselves. Electrocardiograms are to be published by dr B. LANDTMAN in his monograph on arrhythmias in childhood (suppl. Acta Paediatrica).

Ein Fall von imbezillen Zwillingbrüdern.

Von

AINO YLIRUOKANEN.

In der Erbliehkeitsfrage ist die Zwillingsforschung in den letzten Jahren sowohl bei den Ärzten als auch bei den Psychologen zentral gewesen. Die Erbliehkeit hat in der Entwicklung des Intellekts grosse Bedeutung, und nach vielen Autoren ist die Schwachsinnigkeit eine rezessive Eigenschaft, deren Möglichkeit zur Manifestation sehr gross ist (BRUGGER, JUDA, LUXEMBURGER, PLEGER u. a. m.). Nach HOFMEIER sind 4/5 der Schwachsinnigen auf endogenem Boden entstanden, wobei die exogenen Faktoren sehr im Hintergrund stehen. SMITH hat in seinen Zwillingsuntersuchungen folgendes festgestellt: 50 Paare zweieiige Zwillinge (ZE), von welchen in 4 Fällen beide schwachsinnig waren und in 46 Fällen nur der eine Zwilling. 3 Paare eineiige Zwillinge (EE), die alle 6 schwachsinnig waren. 13 Paare waren wahrscheinlich eineiig, davon in 11 Fällen beide schwachsinnig, und nur in 2 Fällen nur der eine. Die Ursache für die Schwachsinnigkeit ist in viel grösserem Masse in der Erbanlage zu suchen als im Einfluss der Verhältnisse. Was das Vorkommen von Zwillingen und Schwachsinnigkeit im Vergleich zueinander betrifft, so scheint z. B. nach JUDA die Anzahl der Zwillinge in den Hilfsschulen deutlich grösser zu sein. Er hebt besonders den grossen Anteil der Erbanlage hervor. Die eineiigen Zwillinge sind praktisch genommen alle konkordant, welche Beobachtung auch LUXEMBURGER gemacht hat. In 40 % der Fälle, in welchen organische Gehirnläsionen festgestellt wurden, befanden sich in der Familie schwachsinnige oder schwach begabte Individuen.

Auch u. a. PLEGER und LOOFT haben unter den Schwachsinnigen mehr Zwillinge festgestellt als unter den normalen Kindern, weshalb sie besonders die Erbanlage betonen.

In der Erbanlage der Schwachsinnigen seien als einige von den wichtigsten Faktoren ausser der einfachen Schwachsinnigkeit (Oligophrenia) auch Epilepsie, Alkoholismus der Eltern und Lues erwähnt. PLEGER hat festgestellt, dass die Belastung der übrigen psychischen Anomalien ungefähr die gleiche ist wie im allgemeinen durchschnittlich, nur Schizophrenie kommt weniger vor.

Die Wirkung der peristatischen oder Umgebungsfaktoren beginnt schon im fötalen Stadium und bei der Geburt, wo die dadurch hervorgerufenen Läsionen beträchtlich auf das Zentralnervensystem einwirken können. Zur gleichen Gruppe der exogenen Faktoren gehört die vorzeitige Geburt. Bei den jungen Frühgeburten ist die geistige Entwicklung im allgemeinen verspätet, und bei einem bedeutenden Teil der Frühgeburten, besonders bei den kleinsten, werden im späteren Alter verschiedene cerebrale Störungen beobachtet (YLPPÖ). BRANDER hat die Beziehung der Geburtstraumen und der Frühgeburt zur Schwachsinnigkeit untersucht. Er bemerkt, dass bei den Frühgeburten sehr viele Geburtskomplikationen vorkommen. Deshalb sind bei der Untersuchung der Ätiologie solcher cerebraler Affektionen, die sowohl auf endogenem Boden als auch auf Grund von mit Geburtstraumen zusammenhängenden peristatischen Faktoren entstehen können, unbedingt in erster Linie die primären obstetrischen Faktoren zu berücksichtigen. Ein beträchtlicher Teil aller Zwillinge wird vorzeitig geboren. Bei der Geburt wirken die ungünstigen Faktoren konkordant und können zu konkordanten Störungen führen, die auf exogenem Boden entstanden sind. Dies könnte bei eineiigen Zwillingen auch für die Erblichkeit sprechen. Bei Kindern mit geringem Geburtsgewicht ist die Entwicklung der Intelligenz im allgemeinen besser als in denjenigen Fällen, wo Geburtstraumen und Erbanlage Nebenfaktoren darstellen. Die Geburtskomplikationen im Zusammenhang mit vorzeitiger Geburt scheinen hinsichtlich der Schwachsinnigkeit weniger gefährlich zu sein als die Kombination erbliche Belastung

und Frühgeburt. SIEMENS und WEITZ haben Fälle veröffentlicht, wo von eineigen Zwillingen derjenige weniger begabt ist, der die geringere Schädelkapazität hat (nach BRANDER). Unter den Fällen von ROSANOFF und IMMAN-KANE ist die Anzahl der Zwillinge unter den Schwachsinnigen recht hoch. Auch Kinder, die als Frühgeburten geboren waren, oder deren Geburtsgewicht niedrig war, kamen unter den Schwachsinnigen 5 mal mehr vor als unter den gesunden.

Das hier zu beschreibende Zwillingspaar ist im Kinderkrankenhaus der Universität Helsinki am 5.7. 45—9.7. 45 untersucht worden.

Nr. 856 und 857/1945. Diagn. Imbecillitas. Scabies.

Zwillingsskaben Olavi (Kind a) und Juhani (Kind b). Geb. 1.1. 40, Söhne eines Landwirts.

Anamnese (von der Mutter und den Bekannten der Eltern): In der Familie keine Geisteskrankheiten, Epilepsie oder Alkoholismus. Der Bruder der Mutter ist »beschränkt«, ist jedoch imstande, sich durch leichte Landarbeit zu ernähren. Sonstige Schwachsinnige sind unter den näheren Verwandten, soweit bekannt, nicht vorhanden. In der Familie der Mutter kommt viel Tuberkulose vor. Mutter geboren 1910, leidet an Augentuberkulose. Geistige Entwicklung der Mutter normal, Charakter sehr misstrauisch und verschlossen. Der Intelligenzindex ist nach LESKINENS Intelligenzuntersuchungs-Methode über dem Durchschnitt. Der Vater war erfolgreich als Landwirt tätig, ist im Kriege 1940 im Alter von 35 Jahren gefallen. Morbi ven. neg.

Das körperliche Befinden der Mutter war zu Beginn der Schwangerschaft gut, aber während der ganzen Gravidität wurde sie von krankhaftem Misstrauen belastigt. Die Entbindung fand 2 Wochen vor der berechneten Zeit in einer Gebäranstalt statt. Die Ursache für die vorzeitige Geburt war ein »Erschrecken« der Mutter, wonach die Wehen begannen. Die Entbindung dauerte wegen Wehenschwäche 3 Tage, ging aber spontan vor sich. Die Kinder wurden in Hinterhauptshaltung geboren und waren sofort nach der Geburt munter. Geburtsgewicht: a 2 500 g und b 2 280 g.

Die Kinder erkrankten im ersten Monat an Nabelentzündung sowie Schnupfen und Ohrenentzündung. Beide hatten Eiterausfluss aus beiden Ohren, der bei a bis zum Alter von 2 Jahren anhielt, b hatte ausserdem Eiterherde am Kinn und hinter den



Ohren, weshalb er im Alter von 2—3 Monaten 2 mal im Krankenhaus war. Im Alter von 2—3 Monaten wurde bei beiden Rachitis festgestellt, und beide hatten Milchschorf. Kind b wurde im Alter von 1 Jahr und 10 Monaten wegen Nabelbruch operiert, und a hatte gleichzeitig Diphtherie. Beide befanden sich gleichzeitig im Krankenhaus und waren nach der Entlassung schwach.

Über die früheste Entwicklung der Kinder kann die Mutter

keine genauen Angaben machen, »weil die Kinder die ersten waren, und die Mutter früher niemals kleine Kinder gepflegt hatte«. Die ersten Zähne brachen ungefähr im Alter von 10 Monaten durch. Die Kinder begannen im Alter von einem Jahr zu kriechen und etwas später mit Stütze zu stehen. Im Alter von ca. 1 Jahr und 10 Monaten konnten sie allein gehen, aber infolge ihrer Krankheit vergassen sie diese Fertigkeit und lernten sie erst im Alter von über 2 Jahren von neuem. Die ersten Worte: »Mutter, gib«, lernten die Knaben 2-jährig sprechen. Erst nachdem sie das 5. Lebensjahr überschritten hatten, konnten sie 2—3 Worte hintereinander sagen, aber auch jetzt (5½-jährig) können sie noch keine vollständigen Sätze bilden. Sie verstehen einfache Dinge, und haben 5-jährig selbst gegessen, was aber recht unreinlich vor sich ging. Noch im Alter von 4 Jahren liessen sie sowohl den Urin als auch die Fäzes unter sich gehen, und erst seit einem halben Jahr können sie bei Tage um den Topf bitten, aber nachts beschmutzen sie ihre Betten immer noch. Sie sind sehr lebhaft, lieben einander sehr und kommen gut miteinander aus. Kind b ist vielleicht lebhafter, a aber energischer.

Status somaticus: Die Ähnlichkeit im Aussehen ist fast vollkommen (Lichtbild). Haar hellbraun, die Wirbel auf dem Kopf gleich. Augen blaugrau. Konstitution am ehesten asthenischer Typ. Kind a wiegt 22,1 kg, Körperlänge 117 cm, Brustumfang 57,5 cm, Bauchumfang 54 cm. Bei b entsprechend Gewicht 19,9 kg, Körperlänge 116 cm, Brustumfang 54 cm und Bauchumfang 50 cm.

Ernährungszustand ziemlich gut. Tonus und Trugor gut. Haut: Gesicht und Hals gebräunt, Wangen rot, Elastizität und Feuchtigkeit normal. Beide haben am Körper Scabies. Vergrösserte Lymphdrüsen nicht palpabel. Schilddrüse normal.

Knochengerüst: Kopf eiförmig oval. Bei a Umfang 52 cm, anteposteriorisches Mass 17,5 cm. Bei b Umfang 50,5 cm, anteposteriorisches Mass 17 cm. Zähne: Bei a 10/9, 1- fehlt, -1 bleibend. Caries 5+ und 5—. Bei b: 10/10, Caries 4+, +4, 5—, 4—, —4, —5. Form des Gaumens normal. Brustkorb schmal. Deutliche Hühnerbrustbildung bei beiden. Gliedmassen gesund.

Zirkulationsorgane: Herz ohne Befund. Bei a: Blutdruck 98/60, Puls 96/Min. Bei b: Blutdruck 90/48, Puls 92/Min.

Respirationsorgane: Ohne Befund.

Verdauungsorgane: Bei a: Tonsillen von der Grösse einer kleinen Nuss, glatt, nicht hypertrophisch. Bei b: Hypertrophisch, ungefähr von der Grösse einer Walnuss, berühren einander fast. Sonst nichts Besonderes.

Nervensystem: Bewusstsein klar. — Keine Nacken- oder Rückensteifheit. Gehen und Laufen unbeholfen, Mitbewegungen normal. Zur Untersuchung der Ausführung der Bewegungen verhalten sich beide widerstrebend. Keine Lähmungen und keine Spastizität. Reflexe normal. Gehirnnerven: Gehör gut, Sehvermögen gut. Pupillen gleichgross, rund, reagieren auf Licht und Konvergenz. Kein Nystagmus. Sprechvermögen: Sagen unvollständige Wörter, stottern aber nicht.

Genitalien: Normal entwickelt.

a: Harn Alb-, Nyl-, Senkungsreaktion 5 mm/Stunde, 15 mm/2 Stunden. Blutbild: Hb 77/90 E 3,63 Mill. Ind. 1,32, Leuk. 5 300, Juv. 0,5 %, Stabk. 1,0 %, Segm. 42 %, Eos. 2,5 %, Mon. 2,5 %, Lymph. 51 %. Röntgenbild: Cor. et pulm. ohne Befund. *Nackenpunktion:* Klar, Pandy-, Nonne-, Zellen 6/mm³, Erytroz. 1 040/mm. WaR-, Kahn-.

b: Harn Alb-, Nyl-, Senkungsreaktion 7 mm/1 Stunde, 8 mm/2 Stunden. Blutbild: Hb 74/93, E 4,60 Mill., Ind. 1,03, Leuk. 5 800, Juv. 0,5 %, Stabk. 1,0 %, Segm. 30 %, Eos. 6,5 %, Mon. 1 %, Lymph. 60 %. Röntgenbild: Cor. et pulm. ohne Befund. *Nackenpunktion:* Klar, Pandy-, Nonne-, Zellen 1/mm, WaR-, Kahn-.

Blutgruppe A. Blutgruppe der Mutter desgleichen A.

Status psychicus: Kind a (Olavi): Am ersten Tag des Aufenthalts im Krankenhaus verängstigt, scheu, negativistisch. Weint oft mit rauher Stimme, besonders bei der Untersuchung schreit es laut. Gesichtsausdruck monoton, starrt oft ausdruckslos mit offenem Mund vor sich hin. Lächeln stereotyp. Führt einfache Bewegungen aus. Steht auf Aufforderung auf, geht. Versucht auf Aufforderung sich selbst aus- und anzukleiden, was aber schlecht gelingt. Zieht die Kleidungsstücke verkehrt herum an,

bekommt die Knöpfe nicht auf oder zu. Isst selbst, aber sehr unreinlich. Lässt Urin und Fäzes bald ins Bett, bald auf den Fussboden gehen. Ist am nächsten Tag beruhigt, reicht die Hand zum Gruss und sagt »Tag«. Lächelt häufiger, aber sehr ausdruckslos. Bei der Untersuchung ist fast gar keine Furcht mehr wahrzunehmen. Der Patient liebt seinen Zwilling Bruder sehr. Als man ihn zum Photograph führt, betrachtet er verwundert die Lampen an der Decke (sagt: »Zwei Lampen«), den Photographenapparat und andere Gegenstände im Zimmer (in der Poliklinik des Krankenhauses). Die Kinder stellen sich auf Aufforderung vor die Kamera, und die ganze Angelegenheit macht ihnen sichtlich Vergnügen, aber ganz unvermittelt klopf Patient a seinem Bruder freundlich auf die Schulter, was dieser sofort in gleicher Weise erwidert. Am nächsten Tag verhalten sie sich zu fremden Leuten nicht mehr ängstlich, und die Knaben sind bisweilen sogar ganz lustig.

Kind b gleicht seinem Bruder fast wie ein Spiegelbild bis zum Gesichtsausdruck, ja sogar zu den Bewegungen. Anfangs ist er jedoch noch furchtsamer und versucht sich bei der Untersuchung zu verstecken. Es hat den Anschein, dass Kind a der führende Typ ist. Das Sprechen beschränkt sich bei beiden auf einige Wörter (vielleicht 20), nämlich die Bezeichnungen der gewöhnlichsten Gegenstände. Die Kinder können höchsten 2 Wörter hintereinander aussprechen, und auch diese unvollständig z. B. »lattialle lu« (lattialle putosi lusikka) (zu Deutsch: »Auf dem Fussboden Lö« = der Löffel ist auf den Fussboden gefallen). Die Wörter sind höchstens 2-silbig, und entweder am Anfang oder am Ende des Wortes bleibt eine Silbe oder ein Buchstaben weg.

Intelligenzproben:

Kind a:

Nach SIMON-BINET ist das Intelligenzalter unter 2 Jahren.

- | | |
|--|---|
| 1. Zeigt Mund, Augen und Nase | + |
| 2. Wiederholung eines 6-silbigen Satzes | — |
| 3. Wiederholung zweier Zahlen | — |
| 4. Aufzählung von Gegenständen nach einem Bild | + |
| 5. Familienname | — |

Die Aufzählung der Gegenstände nach einem Bild gelang teilweise. Das Kind kennt die gewöhnlichsten Haustiere, desgleichen die gewöhnlichsten Gegenstände: Eine Uhr, ein Auto, eine Flasche, einen Löffel. Alle Bilder, die einen Menschen darstellen, nennt das Kind Junge oder Mädchen, ohne verschiedene Altersklassen voneinander unterscheiden zu können. Es kann die Stimmen der gewöhnlichsten Haustiere nachahmen, z. B. des Hundes, der Katze, des Schafs, der Kuh und des Pferdes. Es kennt die Farben nicht, und kann nach einer Vorlage z. B. einen Kreis nicht zeichnen, sondern zieht nur unbestimmte Striche.

Kind b: Das gleiche Resultat wie bei dem Bruder.

Nach BÜHLER-HETZER entspricht die Intelligenz 2 Jahren.

1. Es gelingt schwerfällig, einen Stuhl zu besteigen.
2. Wechselspiel mit einer Uhr abwechselnd rechts und links unsicher.
3. Zählt Gegenstände richtig auf.
- 4.—6. nicht ausgeführt.
7. Es gelingt, Bauklötzchen aufeinander zu setzen.
8. Betrachtung einer Figur, die ein anderer aus Klötzchen gebaut hat: Das Kind zeigt ein wenig Interesse, aber der Gesichtsausdruck ist inhaltslos.
9. Kann einen Stock nicht zu Hilfe nehmen, um einen Gegenstand näher zu bekommen.
10. Erkennt in einem Buch ein bestimmtes Bild, das er, wenn es nach ca. 15 Minuten von neuem gezeigt wird, genauer betrachtet.

Bedauerlicherweise war der Aufenthalt der Kinder im Krankenhaus zu kurz, um die Prüfung von neuem durchführen zu können.

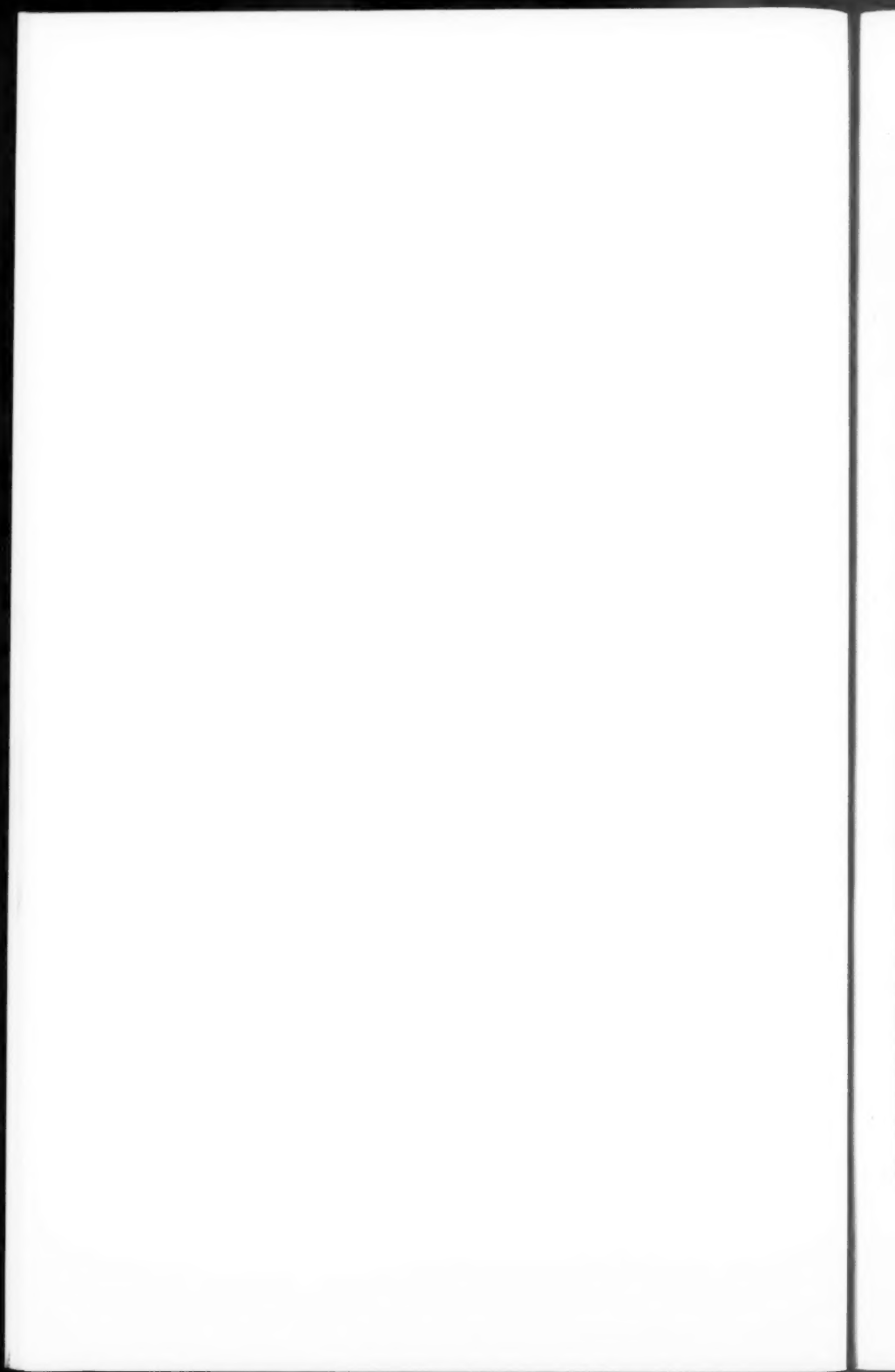
Zusammenfassung.

Der somatische Status des beschriebenen Zwillingspaars weist wesentlich darauf hin, dass es sich um identische, eineiige Zwillinge handelt: Gesichtszüge, Haarfarbe und Wirbel, Farbe der Iris, Blutgruppe. In den Körpermassen bestehen Unterschiede, die mit dem Unterschied des Geburtsgewichts im Verhältnis stehen. Die Masse des Kopfes sind normal. Die Spuren der Rachitis am Brustkorb sind bei beiden Patienten gleich.

Der Status psychicus ist bei beiden so gleich, dass sich im Grad der Intelligenz oder dem Ausdruck der verschiedenen seelischen Funktionen keine nennenswerten Unterschiede wahrnehmen lassen. Irgendein exogenes, mit der Geburt verbundenes Trauma ist ätiologisch nicht festzustellen. Hereditär ist Oligophrenie (Debilitas) des Bruders der Mutter zu berücksichtigen, was zu der Schlussfolgerung berechtigt, dass unsere Zwillinge auf endogenem Boden entstandene Oligophrene (Imbezillen) sind. Der hier beschriebene Fall ist als ein gutes Beispiel für erbliche endogene Oligophrenie zu betrachten, aus deren Ätiologie die exogenen Faktoren eliminiert werden konnten.

Schrifttum.

- BRANDER, T.: Über die Zwillingsforschung und ihre Berührungspunkte mit der Kinderheilkunde. Acta paed. XXI 1937 5—141. Über die Bedeutung des Partus praematurus für die Entstehung gew. cereb. Affektionen u. s. w. Acta paediatr. 12 1927. 313—332. Vem är imbecill. F. L. H. 1936. Studien über die Entwicklung der Intelligenz bei Frühgeborenen Kindern. Soc. Scient. Fenn. Helsinki 1936. — BRUGGER, C.: Vererbung des Schwachsinn. Fortschritt. Neur. 13 1941 1—8. Ref. Zbl. Kinderheilk. XI 1943. — BÜHLER und HEZER: Kleinkindertests. Leipzig 1932. — DESCODRES, ALICE: Le développement de l'enfant de deux ans. Ref. W. Stern Z. angew. Psychol. 20 1922, 226—234. — HOFMEIER, K.: Die Bedeutung der Erbanlagen für die Kinderheilkunde. Stuttgart 1938. — JUDA, A.: Zur Etiol. des Schwachsinn. Neue Untersuchungen an Hilfsschulzwillingen. Z. Neur. 165. 1939. — LEHTOVAARA, A.: Psychol. Untersuchungen. Annal. acad. scient. Fenn. Helsinki 1938. — LESKINEN, W. F.: Täyskasvuisten älykkyystutkimuksista. Acad. Abhandlung. Helsinki 1941. — LOOFT, C.: L'évolution de l'intelligence des jumeaux. Acta paed. 12. 1931. 41—74. — LUXENBURGER, H.: Zur Frage der Manifestationswahrscheinlichkeit des erbl. Schwachsinn. und der Letalfaktoren. Z. Neur. 135. 1931. — —: Ref. Zbl. Kinderheilk. xxvi. 1932. — MEUMANN, I.: Testpsychologische Unters. an ein- und zweieiigen Zwillingen. Arch. f. d. ges. Psychol. 93. 1935. — PLEGER, W.: Erblichkeitsuntersuchungen an schwachsinnigen Kindern. Z. Neur. 135. 1931. Ref. Zbl. Kinderheilk. xxvi. 1932. — ROSANOFF und IMMAN-KANE: Zbl. Kinderheilk. xxix. 1934. Ref. — SMITH, J.: Das Ursachenverhältniss des Schwachsinn. beleuchtet durch Untersuchungen von Zwillingen. Z. Neur. 125. 1930. Ref. Zbl. Kinderheilk. xxiv. 1930. — STERN und WIEGMANN, C.: Methodensammlung zur Intelligenzprüfung von Kindern und Jugendlichen. Leipzig 1926. — YLPPÖ, A.: Pathologie der Frühgeborenen einschliesslich der debilen und lebensschwachen Kindern. Pfaundler-Schlossmann: Handbuch der Kinderheilkunde I. 4. Auflage. Berlin 1931.



Acta Chirurgica Scandinavica. *Editorial Board:* in Denmark P. N. Hansen, S. Kjærgaard; in Finland R. Faltin, F. Langenskiöld; in Norway J. Holst, J. Nicolaysen; in Sweden E. Key (Editor), G. Petré; in Iceland G. Thoroddsen, Reykjavik. Subscription: 25 Sw. crowns. Address: Tryckerigatan 2, Stockholm.

Acta Dermato-Venereologica. *Editorial Board:* in America H. Goodman; in Czecho-Slovakia F. Šamberger; in Denmark C. Rash; in England H. Mac Cormac; in Holland S. Mendes Da Costa; in Norway H. P. Lie; in Sweden J. Almkvist, Sven Hellerström (Editor); in Switzerland Ch. Du Bois. Subscription: 25 Sw. crowns. Address: Sturegatan 22, Stockholm.

Acta Medica Scandinavica. *Editorial Board:* in Denmark H. I. Bing, K. Faber, Eggert Möller, C. Sonne, Erik Warburg; in Finland Gösta Becker, R. Ehrström, Östen Holsti, F. Saltzman; in the Netherlands A. A. Hijmans van den Bergh, W. A. Kuenen, L. Polak Daniels, P. Ruitinga, I. Snapper; in Norway Olav Hanssen, S. B. Laache, H. A. Salvessen, Olav Scheel; in Sweden G. Bergmark, I. Holmgren (Editor), Sven Ingvar. Subscription: 20 Sw. crowns in the Scandinavian countries and 25 Sw. crowns in other countries. Address: Acta Medica Scand., Stockholm.

Acta Obstetrica et Gynecologica Scandinavica. *Editorial Board:* in Denmark E. Hauch; in Finland S. E. Wichmann; in Norway A. Sundé; in Sweden Erik Ahlström (Editor). Subscription: 25 Sw. crowns. Address: Stockholm 5.

Acta Oto-Laryngologica. *Editorial Board:* in Denmark E. Schmiegelow; in Finland Y. Meurman; in Holland H. Burger; in Norway F. Leegaard; in Sweden G. Holmgren (Editor), G. Öhngren; in Switzerland F. R. Nager; in Hungary Z. de Lénárt. Subscription: 25 Sw. crowns. Address: Hospital Sabbatsberg, Stockholm.

Acta Odontologica Scandinavica. *Editorial Board:* in Denmark E. Faber; in Finland J. Kivimäki; in Norway O. Grythe; in Sweden G. Y. Hildebrand (Editor). Subscription: 20 Sw. crowns. Address: Tryckerigatan 2, Stockholm.

Acta Pædiatrica. *Editorial Board:* in Denmark Bent Andersen, Ouf Andersen, C. E. Bloch, P. Plum; in Finland P. Heiniö, V. Rantasalo, C.-E. Riihå, T. Salmi, Arvo Ylppö; in Holland E. Gorter, Cornelia de Lange, J. van Lookeren Campagne; in Norway Th. Frølich, Leif Salomonsen, L. Støttenberg, A. Sundal, Kirsten Uthelm-Toverud; in Sweden C. Gyllenswärd, A. Lichtenstein (Editor), N. Malmberg, Sture Sjöwe, Arvid Wallgren, Wihl. Wernstedt, Y. Åkerrén. Subscription: 25 Sw. crowns. Address: Polhemsgatan 30, Stockholm.

Acta Radiologica. *Editorial Board:* in Denmark P. Flemming Møller, A. Reyn; in Finland C. G. Jansson, G. A. Wetterstrand; in Holland L. G. Heilbron, J. W. S. Henkensfeldt Jansen; in Norway S. A. Heyerdahl, H. Thue; in Sweden L. Edling; in Switzerland R. Gilbert, H. Schinz. Editor: G. Forssell; Sophiahemmetts Röntgeninstitut, Stockholm. Subscription: 25 Sw. crowns. Address: Tryckerigatan 2, Stockholm.

Acta Ophthalmologica. *Redactores:* Fredrik Berg, Uppsala, Sven Larsson, Lund, Emil Enroth, Helsingfors, Birger Malling, Oslo, Ejler Holm, København, Hans Ulrik Möller, København, Ingolf Schiøtz, Oslo, Mauno Vannas, Helsingfors. *Edenda curavit:* Ejler Holm, Hans Ulrik Möller. Subscription: Dan. Cr. 35.—.

Acta Orthopaedica Scandinavica. *Fundator:* Patrik Haglund. *Redactores:* P. G. K. Bentzon, Aarhus, O. Chiewitz, København, G. Frising, Lund, Poul Guildahl, København, Sven Johansson, Göteborg, F. Langenskiöld, Helsingfors, E. Platou, Oslo, H. Sundt, Stavren, Norway, H. Waldenström, Stockholm. *Redigenda curavit:* P. G. K. Bentzon, Kathrinebjergvej 2, Aarhus, Denmark. Subscription: Dan. Cr. 35.—.

Acta Pathologica et Microbiologica Scandinavica. *Redactores:* C. G. Ahlström, Lund, H. Holth, Oslo, K. A. Jensen, København, A. Lindau, Lund, Poul Möller, København, Osv. Renkonen, Helsingfors, Georg Waaler, Oslo, Axel Wallgren, Helsingfors. *Redigenda curavit:* Tage Kemp, Tagensvej 14, København. Subscription: Dan. Cr. 35.—.

Acta Pharmacologica et Toxicologica. *Iussu Societatis Pharmacologiae Hafniae Editi. Redactores:* Gunnar Ahlgren, Lund, Erik Jacobsen, København, Armas Vartiainen, Helsinki. *Redigenda curavit:* Knud O. Møller, København. Subscription: Dan. Cr. 35.—.

Acta Psychiatrica et Neurologica. *Redactores:* Nils Antoni, Stockholm, B. Brouwer, Amsterdam, E. Essen-Møller, Lund, Harald Fabritius, Helsingfors, Mogens Fog, København, Hjalmar Helweg, København, Sv. Ingvar, Lund, G. H. Mourad-Krohn, Oslo, Matti Kaila, Helsingfors, H. Sjöbring, Lund, Cornelis Winkler, Utrecht. *Redigenda curavit:* Knud H. Krabbe, København, Dr. Tværgade 6. Subscription: Dan. Cr. 35.—.

Acta Tuberculosa Scandinavica. *Redactores:* S. Bang, København, Axel von Bonsdorff, Mummela (Finland), J. Heimbeck, Oslo, A. Kristenson, Stockholm, Sig. Magnusson, Reykjavik, H. Møllgaard, København, John Lundquist, Stockholm, Alex. Tuxen, Varde (Norway). *Editor:* Dr. med. Niels Sjørslev, St. Strands-træde 21, København K. Subscription: Dan. Cr. 35.—.

Subscriptions and advertisement for these Acta should be forwarded under the names of the respective Acta, address: Einar Munksgaard, Nørregade 6, Copenhagen. Manuscripts to be forwarded to the Editor or the redigenda curavit.

EINAR MUNKSGAARD — COPENHAGEN

INDEX ACTORUM.

	Pag.
ROLF LUFT: Chorionic Gonadotrophin in the treatment of Disturbances of Development in Childhood and Adolescence	211
JOHAN RIIS: The acute leukemia in children	230
HUGO JELKE: Schönlein-Henochsche Purpura als Komplikation der Diphtheri-Schutzimpfung	245
ARNE NJÄ: A Sex-linked Type of Gargoylism	267
N. HALLMAN: Über das Vorkommen von schwachsinnigen Kindern verschiedener Typen und verschiedenen Alters sowie über ihre Möglichkeiten am Leben zu bleiben	287
DAG RIIS: Pneumothorax, Mediastinal Emphysema and Cutaneous Emphysema complicating Tracheotomy	321
ÅKE FRISK and G. KLACKENBERG: A Study of the Onset and Prognosis of Nephritis in Children	349
SVEND HEINILD: Acute Macrocytic Anemia in the Newborn (with Special Reference to its Relation to Erythroblastosis Foetalis)	373
EDGAR MANNHEIMER: Paroxysmal tachycardia in infants	383
AINO YLIRUOKANEN: Ein Fall von imbezillen Zwillingsbrüdern	391

